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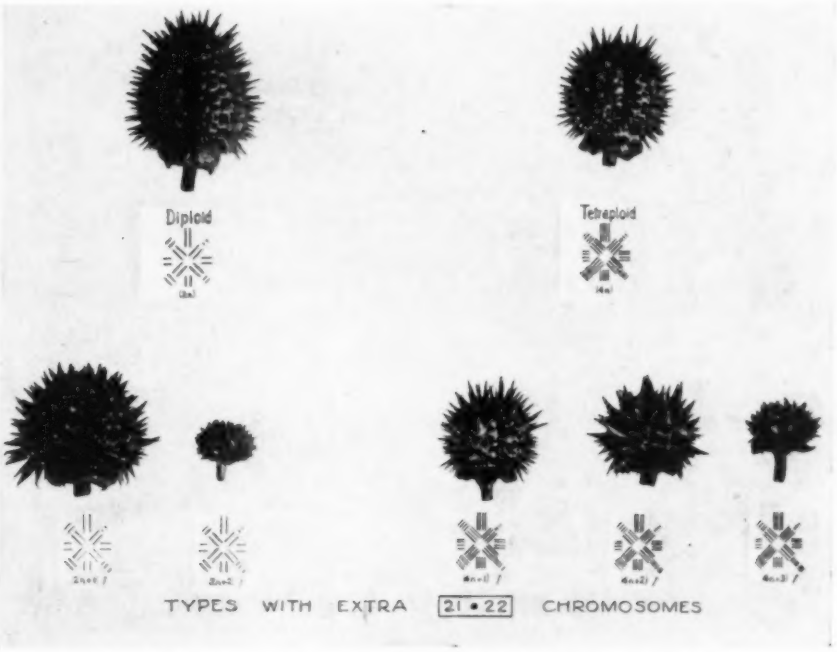

"GLOBE" EXTRA-CHROMOSOME JIMSON WEEDS

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Genetical Contributions to the Study of Evolution

Y-Chromosome Inheritance

Defective Skulls in Swine

The Nature of Susceptibility to Cancer in Mice

Inherited Anomalies of Metabolism

VOLUME 25 MARCH, 1934 NUMBER 3

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An incorporated organization devoted to promoting a knowledge of the laws of heredity and their application to the improvement of plants, animals, and human racial stocks

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The Most-Illustrated Issue of The Journal

This issue of the *Journal* contains 40 illustrations, more than have ever before been published in one number. On the basis of the Chinese proverb which gives one picture the perhaps inflated value of ten thousand words, this copy of the *Journal* represents the verbal equivalent of one of those very large denomination bills which most of us hear about but rarely see.

The series of photographs accompanying Dr. Blakeslee's article is an excellent example of the value of illustrations in recording and interpreting genetic research. The interrelations between the "secondary types," and between these and the "compensating types" whose chromosomal constitution contains the same gene-pills in different chromosome-bottles, could hardly have been as effectively brought out in any other way. The publication of a sufficiently extensive series of illustrations to make a really effective summary of this phase of Dr. Blakeslee's work was made possible by the Carnegie Institution of Washington, which generously furnished the illustrations accompanying this article.

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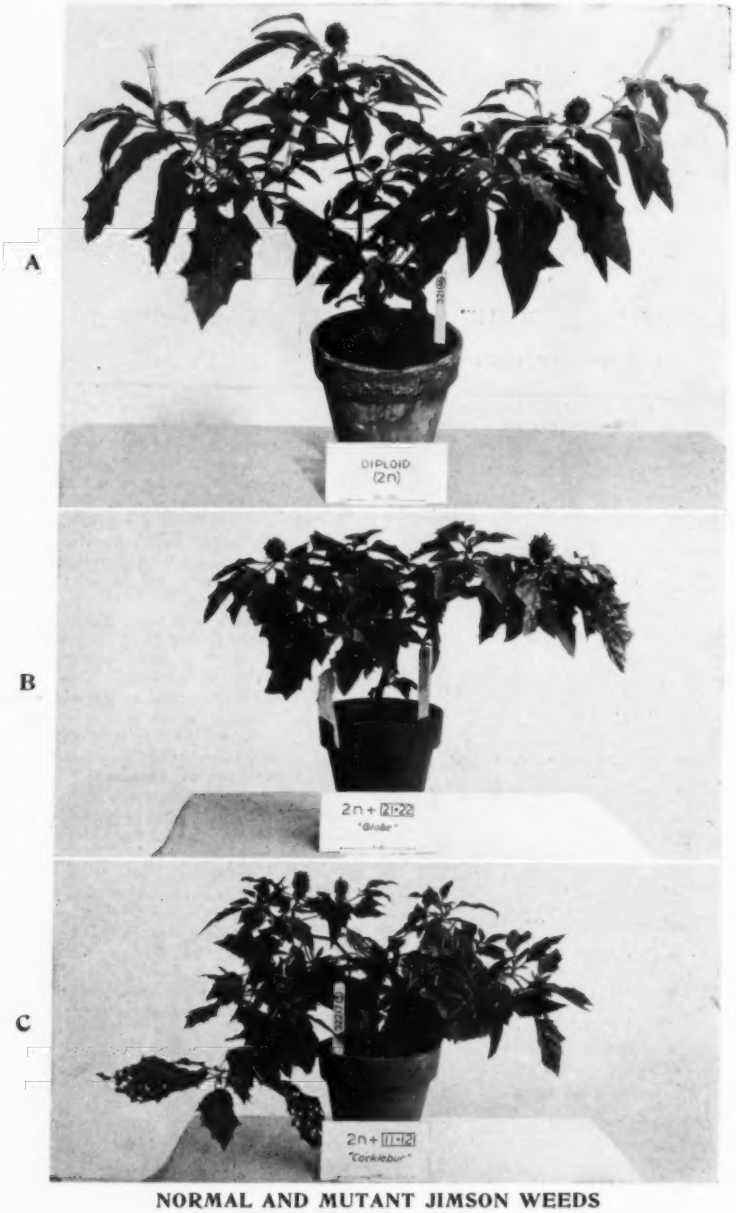


NORMAL AND MUTANT JIMSON WEEDS

Frontispiece

Plants of the normal diploid (*2n*) form (*A*), and of two chromosomal mutations (*B* and *C*). The Globe mutant was the first of these aberrant forms to be discovered. The search for the correct explanation of this new mutation initiated a research that has extended over twenty years and that has had unexpected ramifications. Both the "Globe" (*B*) and "Cocklebur" (*C*) mutants are of the extra-chromosome type. They owe their pecularities to the fact that their cells contain 25 chromosomes instead of the usual 24. The characteristic differences are due to the fact that a different chromosome is extra in the two types. The normal *2n* plant (*A*) has egg-shaped capsules. The "Globe" with an extra 21·22 chromosome (see Figure 8), is characterized by globose capsules. The "Cocklebur" form has an extra 11·12 chromosome and has slender capsules, narrower leaves, and a drooping habit of growth.

NEW JIMSON WEEDS FROM OLD CHROMOSOMES

ALBERT F. BLAKESLEE

*Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, N. Y.**

MOST of those who read this article are familiar with the Jimson Weed. The plant is found in the South and in the corn belt of the Middle West. Its appearance in winter may be seen from Figure 1, which shows a branch with the dried 4-valved fruits. The unripe fruits are egg-shaped, as seen on the greenhouse plant shown in the Frontispiece.

The Jimson Weed, which has the scientific name of *Datura stramonium*, was first grown by us more than twenty years ago to illustrate Mendel's law of inheritance to students at the Connecticut Agricultural College.† In 1915, my assistant, Mr. B. T. Avery, called my attention to a plant with globose capsules and with broader leaves than normal. To this mutant we gave the name of "Globe." A potted plant of the Globe type is shown in Frontis. (*B*) Later at the Carnegie Institution's Station for Experimental Evolution, another mutant type named "Cocklebur" was discovered which was characterized by a spreading habit of growth and small narrow capsules as may be seen in the Frontispiece (*C*). Ultimately a number of mutant types were discovered in cultures of this species, all of which showed abnormalities in the manner of their inheritance which suggested the desirability of studying their chromosomes for a possible clue to their peculiar behavior.

We were fortunate in securing the cooperation of Dr. John Belling (Figure 2) whose recent death has deprived biology of one of its most careful and brilliant students of the relation between chromosomes and heredity. Belling solved the immediate problem of the Globe and the Cocklebur mutants but opened up further problems of more general interest upon which we are still working.

Perhaps not all are as familiar with chromosomes as they are with Jimson Weeds, although they may have heard them spoken of as the bearers of hereditary characters. It may not be amiss, therefore, to introduce the subject with a series of diagrams. Figure 3 is a diagram of a Jimson Weed with its chromosomes shown at the right. All the cells throughout the plant contain rod-shaped bodies called chromosomes (literally colored bodies) because they retain the color strongly when stained with certain dyes. In the cells of roots, stems, and leaves the chromosomes are in pairs, two of each kind, but in the formation of the sex cells (egg cells and pollen grains) the number is reduced to one half so that these cells have only one of each kind of chromosome.

In the Jimson Weed there are twelve different kinds of these hereditary bodies. In other words, $1n = 12$. The

*From the lecture series on Studies in Heredity given at the Carnegie Institution of Washington, in March, 1933. Other speakers were M. Demerec and H. H. Laughlin.

†It should be stated that the Jimson Weed investigations have been almost from the first a cooperative undertaking. In presenting the work I am acting as spokesman of the group. Dr. Bergner, with Miss Satin, is carrying on the microscopic work with the chromosomes; Dr. Buchholz is studying the behavior of the pollen tubes and Dr. Cartledge the abortion of the pollen grains; Dr. Sinnott is studying the effects of extra chromosomes upon the internal anatomy and Mr. A. G. Avery has charge of the care of the plants and shares the work of recognizing and recording types.

plant which results from the union of the sex cells has twice as many chromosomes, and therefore $2n = 24$. (See Figure 3.) The majority of the chromosomes can be recognized in favorable microscopic preparations by differences in size shown by the diagram and by the presence of humps on ends of certain of the chromosomes. Of course the actual chromosomes are not shaped like these in the diagram nor arranged in such a symmetrical pattern. What they look like in the microscope may be seen by Figure 10 (second row).

We have used another type of diagram in a talk before a group of medical men. Figure 4 shows a photograph of twelve pairs of medicine bottles each containing a single row of pills. The medicine bottles can be compared to the chromosomes and the pills which they contain to the hereditary factors or "genes" which are arranged in a single thread within each chromosome. In the lantern slide used, the different pills were colored differently to indicate that these "hereditary pills" as they may be called, have different potencies and hence have different influences upon the characteristics of the adult organism.

Dr. Demerec has described the "hereditary pills."* It is for me to discuss the "hereditary bottles" or chromosomes but it should be pointed out that the effects which, as we shall explain, are brought about by adding extra hereditary bottles or parts of such bottles are due to the additional hereditary pills which they contain.

We have used several different means of representing chromosomes conventionally. If we may wean you from the bottles, we will carry on the discussion for a while with magnetized models.† Figure 5 shows much the same arrangement of chromosomes as in the bottle diagram. The two ends

A WEED WHICH IS CULTIVATED
Figure 1

Branch of Jimson Weed (*Datura stramonium*) in winter condition, showing four-valved capsules. This humble relative of the potato has been used in the experimental study of evolution. Studies of the plants themselves and of their chromosomes have helped to unravel some of the mysteries of heredity.

*Demerec, M., "What Is a Gene?" *Journal of Heredity*, 24: 369-378.

†The models used were of cardboard attached with shellac to small magnets which could be moved around on an iron blackboard. The magnets and blackboard are obtainable from the Meccano Co. of America, New Haven, Connecticut. The colors used in the lecture to distinguish the different chromosomes have been replaced in the present illustrations by conventional designs in black and white for convenience in reproduction.

DR. JOHN BELLING

Figure 2

Dr. Belling made many contributions to our knowledge of the chromosomes. He was a master of cytological technique, a keen observer and showed rare ability in formulating hypotheses with a strong factual foundation. His theory of segmental interchange between different chromosomes, which was proposed to explain certain abnormalities in the Jimson Weed, has cleared up many enigmas of chromosomal behavior in other forms as well and paved the way for important advances in the study of evolution.

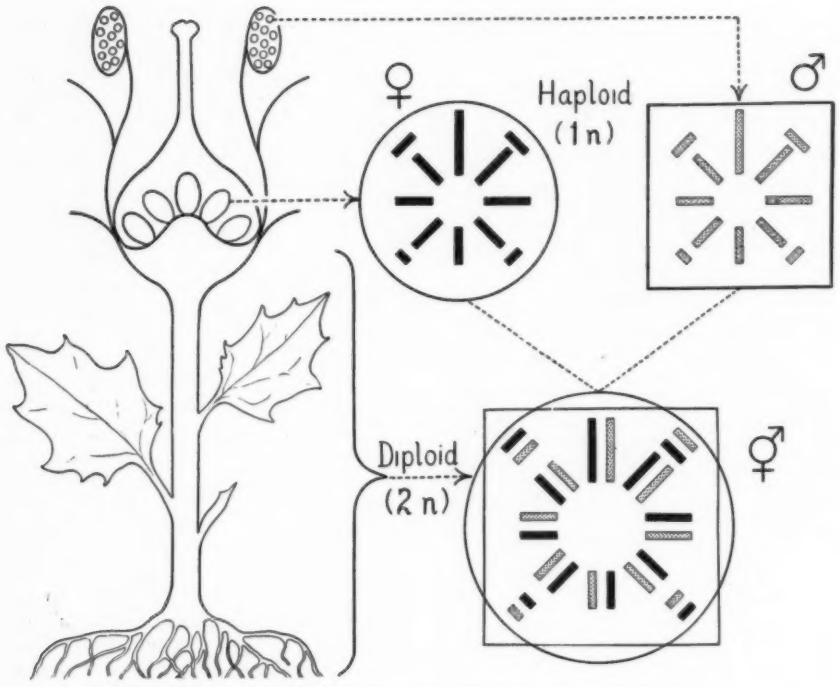
of each chromosome are distinguished by shading one half with diagonal cross lines. Six size classes are represented by differences in length of the models. There is one very large (*L*), two large (*l*), five large medium (*M*), two small medium (*m*), one small (*S*), and one very small (*s*).

We have another shorthand method of representing the chromosomes which distinguishes their ends. They can be shown as dominoes with numbered ends or more simply by two numbers separated by a dot. The largest chromosome is numbered 1·2 [1 · 2] the next chromosome 3·4 [3 · 4] and so on to the smallest chromosome, 23·24 [23 · 24] The odd number is always given to the end which was shaded in the models.

Occasionally a mutant type has appeared in our cultures which a microscopic examination has shown to have an extra chromosome. "Globe," the first mutant type discovered, has an extra chromosome, which is *S*, the next to the smallest chromosome of the 12. It is classed as a $2n + 1$ type and has 25 instead of the normal 24 chromosomes. If we want to be more specific and name the extra chromosome in the formula we can call this type $2n + 21 \cdot 22$.

Since there are 12 different kinds of chromosomes, we might be expected to find 12 different $2n + 1$ types, each with a different chromosome extra. In Figure 6 are shown capsules of these 12 primary $2n + 1$ types. Below each capsule is shown the conventionalized model of the chromosome which is extra with the two ends numbered. At the top of the photograph is shown a capsule of a normal $2n$ plant. It will be noticed that all the capsules are different, due to the increased dosage of hereditary pills in the particular hereditary bottle that is extra. Similar differences would be found in other parts of the plant but capsules are most convenient for representation.

Before going further, it is necessary to explain that there are other types than the normal $2n$ plants to which extra chromosomes may be added. Figure 7 shows diagrams of some of the abnormal chromosomal types in the Jimson Weed. We have classified them into Balanced and Unbalanced Types according to whether or not all the sets have the same number of chromosomes. Since these diagrams represent the condition in the adult plant, only the diploid ($2n$) condition is normal. We need not speak further of the Balanced Types at the present time except to say that all four may be modified by the addition of an extra chromosome. It might be stated that we had never before identified a $1n + 1$ type until recently when Miss Satin confirmed our



REPRODUCTIVE CYCLE IN THE JIMSON WEED

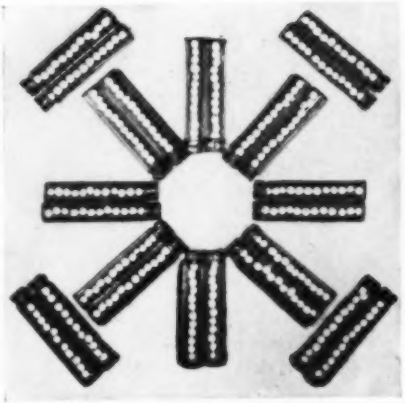
Figure 3

There are twelve kinds of chromosomes represented in the diagrammatic cells at the right. In the vegetative ($2n$) part of the plant, each chromosome is present in duplicate. In male (♂) and female (♀) sex cells, found in pollen grains and ovules, only one chromosome from each pair is present. The extra chromosomes which are discussed in this paper are additions to the normal complement of 24 chromosomes. Unless all the chromosomal material contained in the twelve pairs is present, normal development cannot take place.

suspicions by finding 13 chromosomes in a weak plant from the greenhouse.

The unbalancing effect of extra chromosomes upon a single organ of the plant may be shown by the capsules in Figure 8. Above on the left is shown a capsule of a $2n$ plant which is the normal standard throughout our discussions. The addition of an extra Globe, or 21·22 chromosome, causes the capsule below at the left to be shortened, showing that the assemblage of hereditary pills in the 21·22 hereditary bottle have, among other effects, a depressing influence upon the shape of the capsule. The unbalance here is one extra chromosome against the normal 24. In the adjacent capsule which has two extra 21·22 chromosomes, the unbalance is numerically doubled (2 against 24) and the capsule is still further depressed. Above at the right is a capsule of a $4n$ plant which is typically somewhat more spherical than that of the normal $2n$. The $4n + 1$ capsule below is only slightly depressed in comparison with the $4n$ capsule above. It has, to be sure, a single extra chromosome exactly like that on the extreme left but its unbalance is one against 48 which is numerically half the unbalance of the $2n + 1$ capsule.

As we increase the number of extra



THE CHROMOSOMES REPRESENTED AS BOTTLES

Figure 4

Chromosomes may be compared to "hereditary pill bottles," represented by the paired medicine bottles in the photograph. Each hereditary bottle contains a row of "hereditary pills" (called genes). The pills in each of the bottle pairs are different, and all of them have a function in controlling development.

21·22 chromosomes in the $4n$ series from the $4n + 1$ to the $4n + 3$ type, the depression of the capsule is correspondingly increased but we have not yet obtained a $4n + 4$ Globe plant which would have the same numerical unbalance (4 against 48) as the $2n + 2$ plant with an unbalance of 2 against 24. It makes considerable difference not only how many extra hereditary bottles are added to a plant but also what the constitution of the plant is that we start with.

We have just discussed the $2n + 2$ type in which the two extra chromosomes are alike. Types with two extra chromosomes are known in which the extra chromosomes are different. The capsules in Figure 9 will serve as an example. Above is a capsule of a normal $2n$ and at the right a capsule of the Globe type that we have already discussed. It has the 21·22 or next to the smallest chromosome extra and its formula may be written $2n + 21{\cdot}22$. The capsule on the left was from a $2n + 23{\cdot}24$ type which has the smallest chromosome extra. It is characterized by small capsules and slender spines. The type below is a double or $2n + 1 + 1$ type and has both an extra 21·22 and an extra 23·24 chromosome. The spherical shape, small size and slender spines, are the resultant of the extra dosage of pills from these two added chromosomes. After one becomes familiar with the effects of the pills in the twelve different chromosomes, as seen in the twelve primary $2n + 1$ types, it is relatively easy to determine which two chromosomes are extra in a $2n + 1 + 1$ type, by merely looking at the plant.

How Extra-Chromosomal Types Are Obtained

In any large planting we always expect that a few—not over two in a thousand—will be types with single extra chromosomes. Getting them is a relatively simple process if we have a $4n$ plant to start with. A $4n$ plant, crossed with a normal $2n$, produces $3n$ normal produces all the 12 primary offspring. The latter crossed with a $2n + 1$ types and a large number of double or $2n + 1 + 1$ types. Much depends upon getting $4n$ plants but they have appeared rather frequently in our cultures and can probably be induced by the stimulus of high temperatures.

Although we expected to be able to find 12 distinct types, each with a different extra chromosome, we soon were puzzled by having more than twelve $2n + 1$ types. We noticed, however, that they appeared to form small groups of related forms. A study of the chromosomes in connection with differences in the breeding behavior enabled us to classify our extra chromosomal types. The explanation may be made clearer perhaps, if we refer again to our chromosomal models of Figure 5. For convenience we will center our discussion on the largest or white chromosome which has also been represented by the formula 1·2. In Figure 10, models only of the 1·2 chromosomes need be shown. We

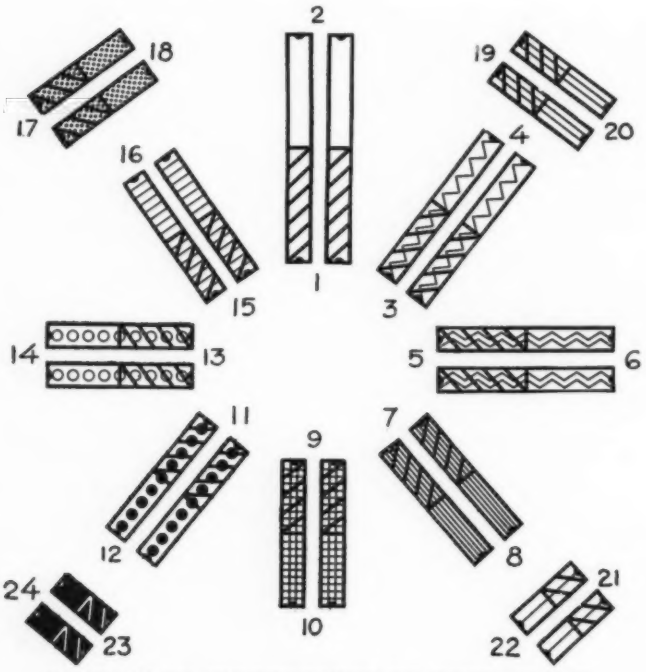


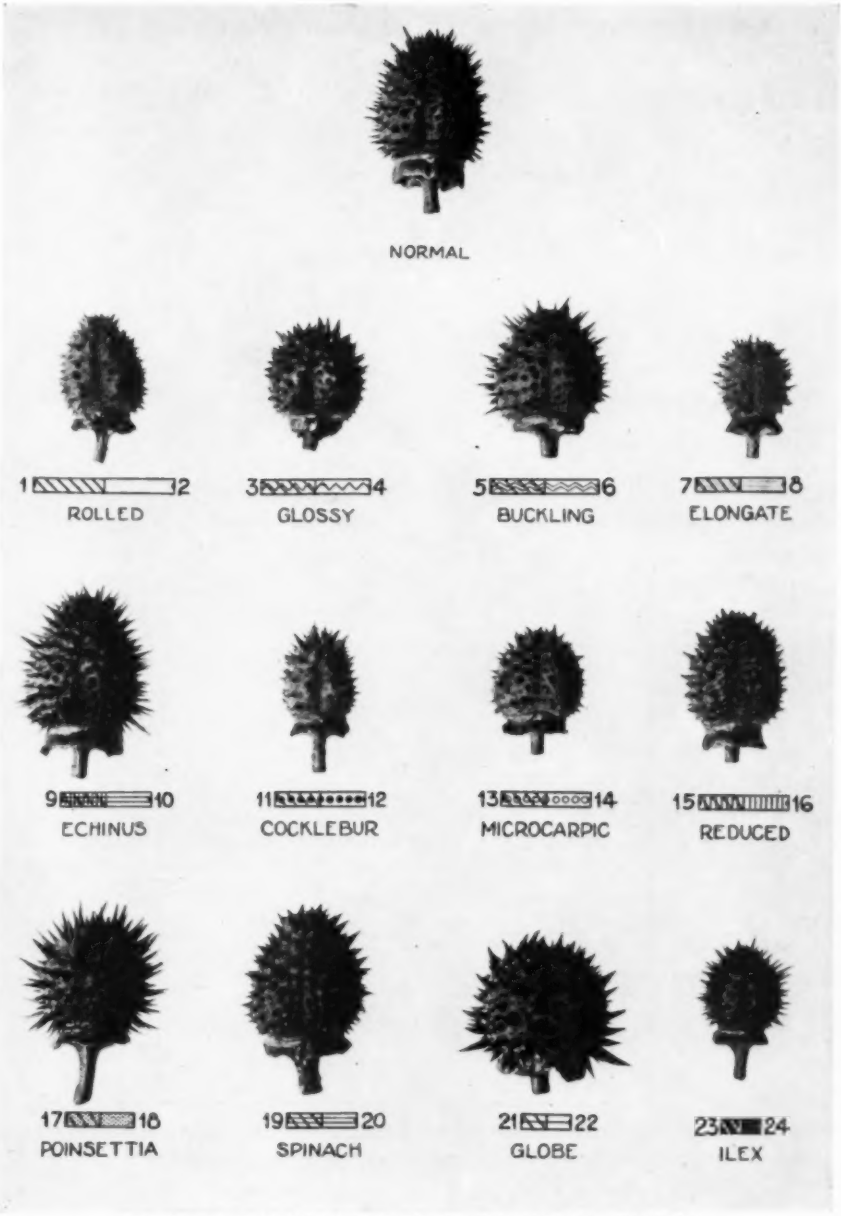
DIAGRAM OF CHROMOSOMES OF JIMSON WEED

Figure 5

The twelve pairs of chromosomes are represented by cardboard models mounted on magnets. Each chromosome has been given a characteristic conventional marking which is used in the illustrations throughout this article. The two halves are distinguished by shading with diagonal cross lines on one end. The two ends are also indicated by numbers, the odd number in each case being assigned to the shaded end. The differences in size correspond to actual differences in the sizes of the chromosomes as seen under the microscope. The largest chromosome is designated 1·2; the smallest 23·24.

may add an extra 1·2 chromosome as shown at base of the middle column and obtain a primary $2n + 1$ plant with peculiarities in appearance which give us some information about the hereditary pills in the 1·2 chromosome. Sometimes apparently two adjacent 1·2 chromosomes break in the middle and reunite in such a way that we have double half chromosomes formed. In terms of our medical models, one of the hereditary bottles will have only tops at the two ends and the other one only bottoms.

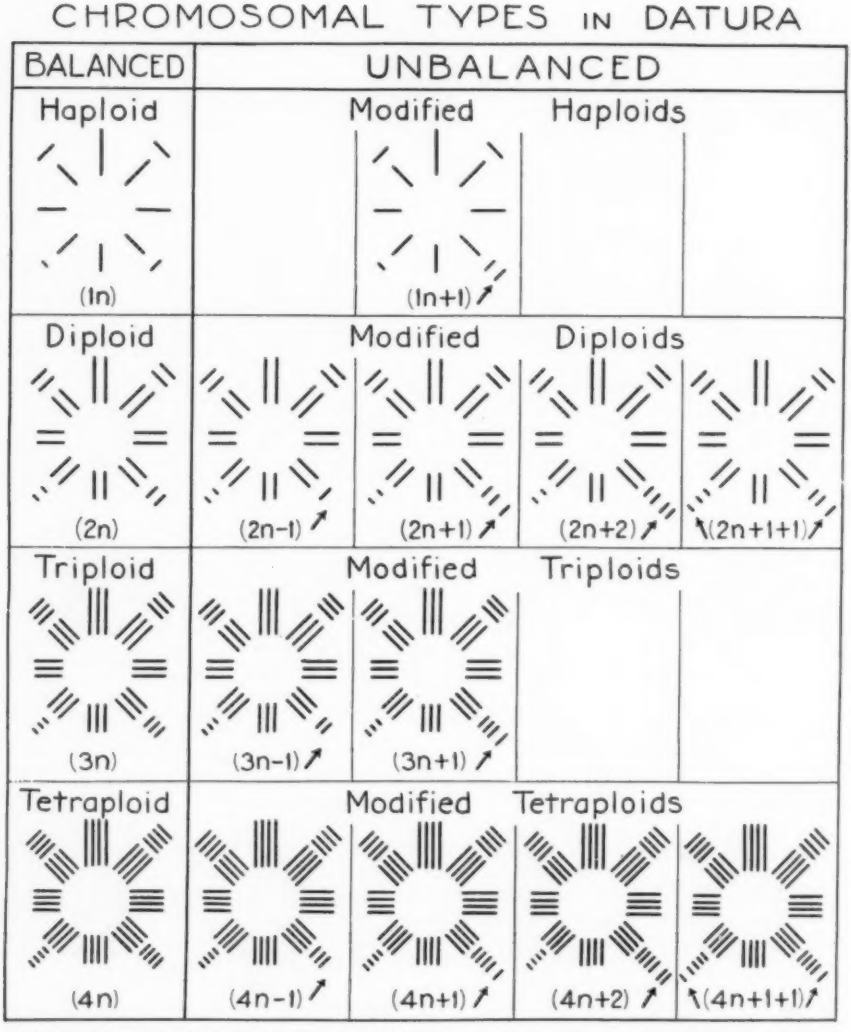
In the left column we have added an extra chromosome which has had the shaded or ·1 half doubled. Such a $2n + 1·1$ type gives us information about the hereditary pills in the ·1 half of the 1·2 chromosome. Similarily on the right, we have added a chromosome made up of the unshaded or ·2 half doubled. This $2n + 2·2$ type gives us information about the hereditary pills in the ·2 half. We can see from the photographs that the ·1 half contains factors which cause the capsule to be small and the leaves narrow while the ·2 half contains factors which make the capsule large, sugarloaf-shaped and short spined and the leaves relatively broad. Such plants, in which the extra chromosome is made up of one half doubled, are called *secondary* $2n + 1$



TWELVE PRIMARY EXTRA-CHROMOSOMAL TYPES

Figure 6

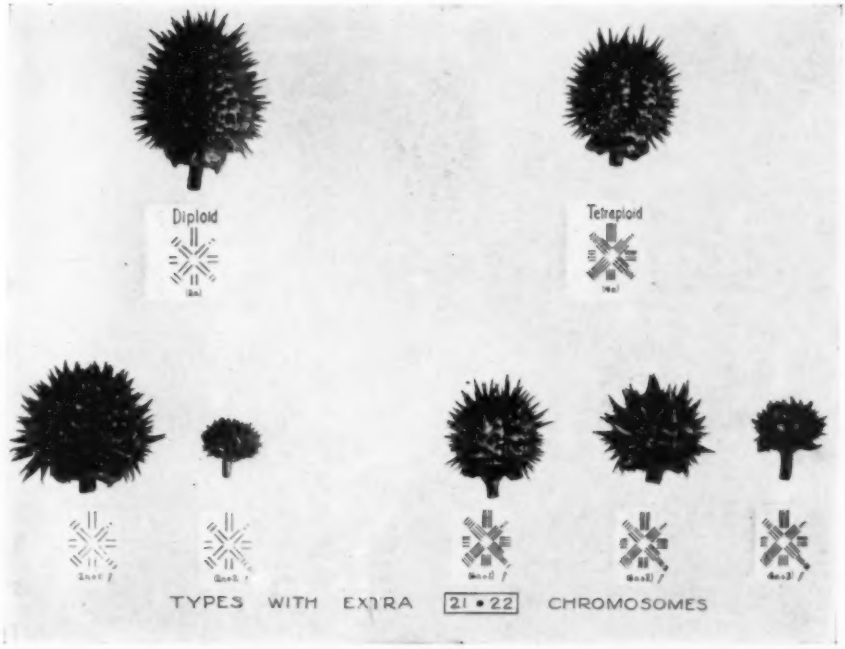
Above, capsule of a normal *2n* Jimson Weed. Below, capsules of the twelve primary *2n* + 1 types each characterized by having a different extra chromosome. Beneath each capsule is given the common name and a numbered model of the extra chromosome which is responsible for the mutant form. The "gene-pills" which are in excess in each of the extra chromosomes influence the development of the capsule in characteristic ways. The whole plant as well as the capsule is affected by the extra chromosomes. (See Figures 13—23.)



DIAGRAMS OF SOME CHROMOSOMAL TYPES FOUND IN THE JIMSON WEED

Figure 7

These diagrams show only some of the kinds of chromosomal mutations which have been found in the course of these studies. For a more complete list see Table III.



CAPSULES OF FIVE "GLOBE" TYPES

Figure 8

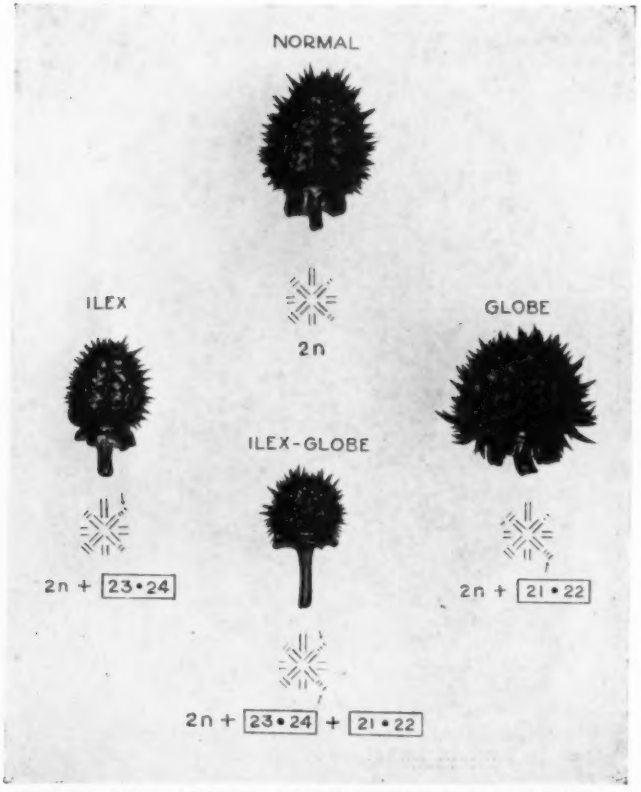
The "Globe" mutants are all characterized by having one or more 21·22 chromosomes extra. The increase in "concentration" of the chromosome results in a progressive intensification of the "Globe" characteristics.

types in contrast to primary types in which the extra chromosome is like the other two in the set.

The plant represented on the left has two extra doses of the ·1 half and hence is highly unbalanced in the ·1 direction. Similarly the plant on the right with two extra doses of the ·2 half is highly unbalanced in the ·2 direction. The plant between them has one extra dose of the ·1 half and also one extra dose of the ·2 half and hence is unbalanced, though to a less degree, in both the ·1 and the ·2 direction. Primary $2n + 1$ types are therefore usually intermediate in appearance between their two secondaries as may be seen from the later illustrations.

Above the models in Figure 10 are shown drawings of the chromosomes as they actually appear in the microscope. They are at the stage of reduction division at which the like ends are connected. The large 1·2 chromosome is marked *L* and is easily distinguished by its size. All the chromosomes are in pairs except the *L* which is in threes. In the secondaries only do the *L*'s form a closed circle of three. The 1·1 chromosome may connect with the two 1·2 chromosomes at the ·1 ends while the 2·2 chromosome may connect with the ·2 ends. In both cases a closed circle of three will result as shown in the drawings, but three 1·2 chromosomes found in the primary can never form a closed circle.

We have seen how we can gain information about the factors in the two halves of chromosomes by the appear-



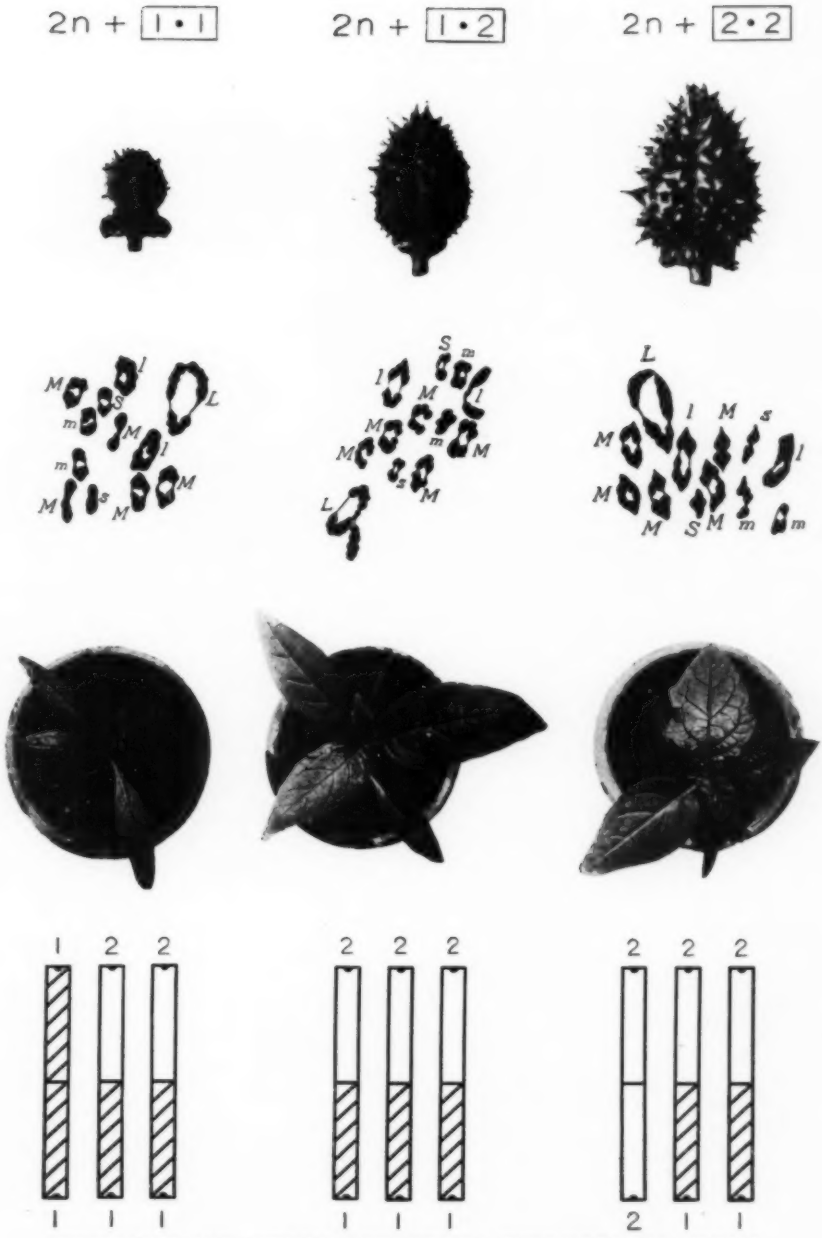
"ILEX" AND "GLOBE" CHARACTERISTICS COMBINED

Figure 9

The "Ilex" form (left) has an extra 23·24 chromosome which produces a different effect from that of an extra "Globe" (21·22) chromosome, (right). Combining these two extra chromosomes in a single individual (below) produces a form that partakes somewhat of the characteristics of both.

ance of the complementary secondary $2n + 1$ types which have the respective halves doubled in the extra chromosome. Unfortunately we do not have both the theoretically possible secondaries for all the chromosomes and in these cases have to depend upon indirect evidence. The primary $2n +$ 17·18 type has characters shown in later photographs, the secondary $2n +$ 17·17 is a dwarfish form with some of the characteristics in its primary emphasized. No $2n + 18{\cdot}18$ plant has been found. The extreme characters of the secondary due to the extra ·17 half can be subtracted from the characters of the primary due to the extra 17·18 chromosome and thus information obtained regarding the factors in the ·18 half. Our information regarding the factors in the ·18 half has been checked in other ways so that we know pretty well what the secondary $2n + 18{\cdot}18$ type would look like if it should ever appear in our cultures.

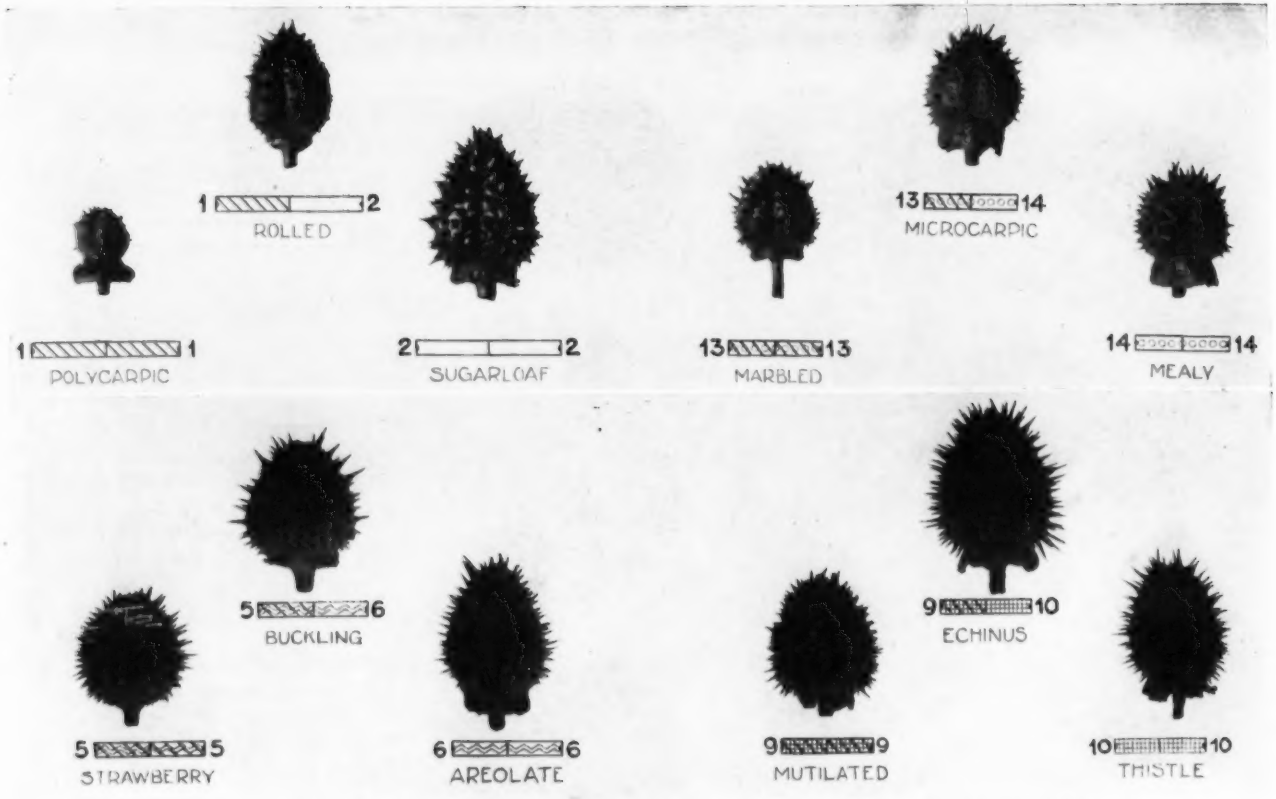
In Figure 11 are shown capsules of four primary $2n + 1$ types with the two secondaries of each. In Figure 12 are shown capsules in cases in which only a single secondary has been found.



"PRIMARY" AND "SECONDARY" EXTRA-CHROMOSOMAL FORMS

Figure 10

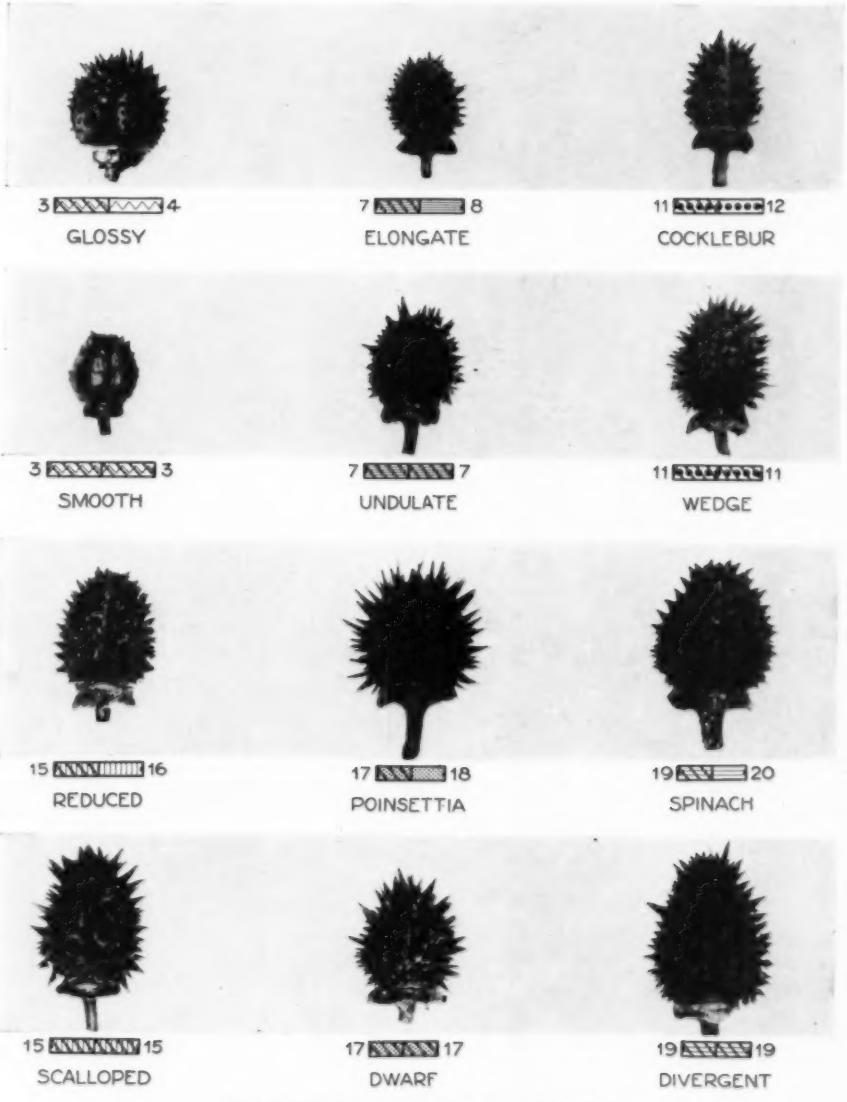
The primary $2n + 1{\cdot}2$ and its two secondaries, $2n + 1{\cdot}1$ and $2n + 2{\cdot}2$. Upper row, capsules; second row, drawings of chromosomes; third row, seedlings; bottom row, models of the *L* chromosomes. Reading from left to right, in the first column appears the plant having the secondary chromosome 1·1 extra called "Polycarpic;" in the second column the unaltered 1·2 chromosome is extra, the plant is called "Rolled"; the third column shows the plant having the 2·2 chromosome extra which is called "Sugarloaf".



PRIMARIES AND SECONDARIES FOR EACH OF FOUR EXTRA CHROMOSOMES

Figure 11

Capsules of four primary $2n + 1$ types, and the two secondaries of each. A numbered model of its extra chromosome is shown below each capsule.

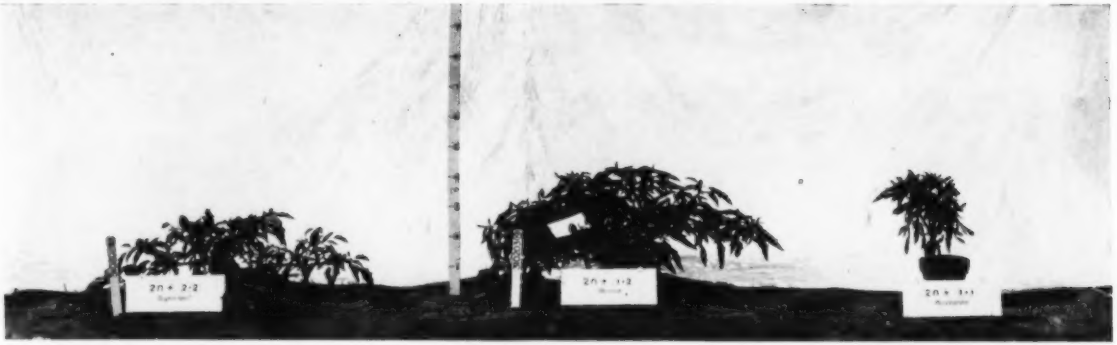


SIX PRIMARY-SECONDARY PAIRS

Figure 12

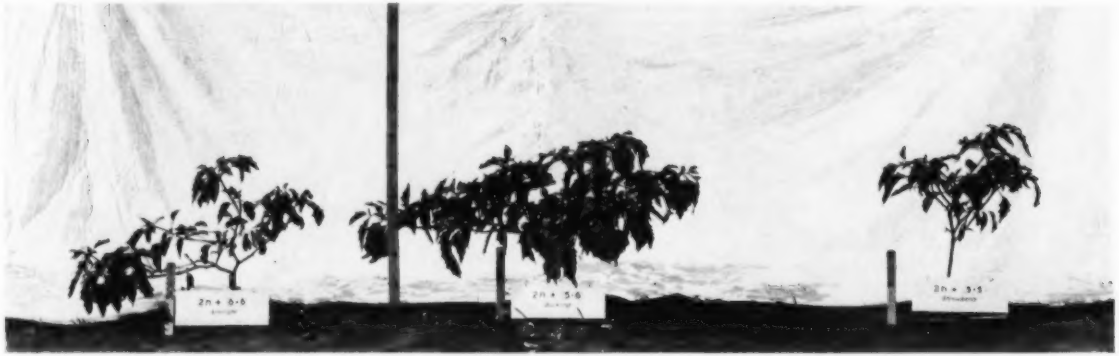
Capsules of six primaries (with an unmodified extra chromosome), and their secondaries. A numbered model of the extra chromosome is shown beneath each capsule.

SECONDARIES PRIMARIES SECONDARIES



"Sugarloaf" ($2n + 2 \cdot 2$) "Rolled" ($2n + 1 \cdot 2$) "Polycarpic" ($2n + 1 \cdot 1$)

Figure 13



"Areolate" ($2n + 6 \cdot 6$) "Buckling" ($2n + 5 \cdot 6$) "Strawberry" ($2n + 5 \cdot 5$)

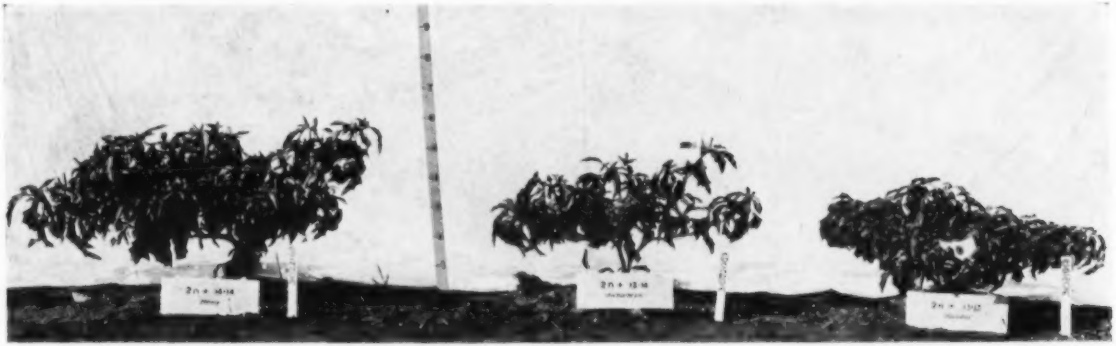
Figure 14

PRIMARY AND SECONDARY TYPES

See legend on opposite page for explanation.

See legend on opposite page for explanation.

SECONDARIES PRIMARIES SECONDARIES



"Mealy" (2*n* + 14·14) "Microcarpic" (2*n* + 13·14) "Marbled" (2*n* + 13·13)

Figure 15

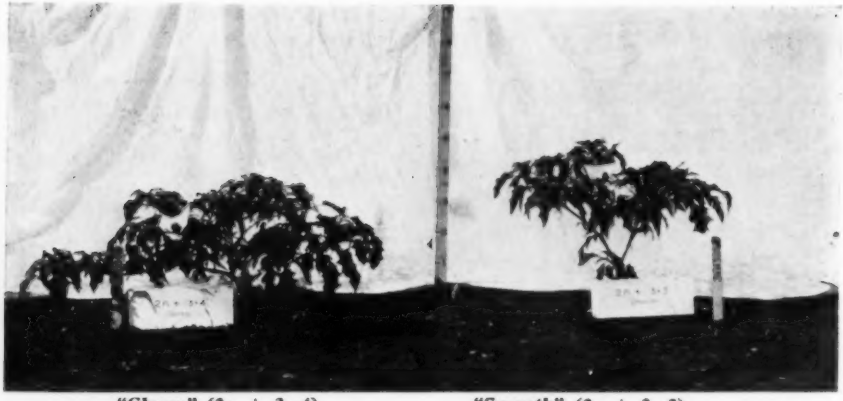
"Thistle" (2*n* + 10·10) "Echinus" (2*n* + 9·10) "Mutilated" (2*n* + 9·9)

Figure 16

PRIMARY AND SECONDARY TYPES

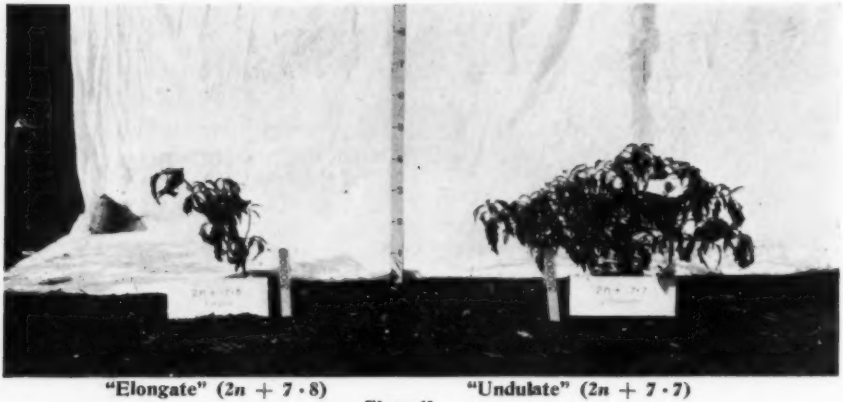
In the center are shown plants of the primary extra-chromosomal forms, each having one unmodified chromosome in addition to the usual complement of twelve pairs. On each side are the two secondary forms, in which the extra chromosome is made up of duplicate half-chromosomes.

PRIMARIES SECONDARIES



"Glossy" ($2n + 3 \cdot 4$) "Smooth" ($2n + 3 \cdot 3$)

Figure 17



"Elongate" ($2n + 7 \cdot 8$) "Undulate" ($2n + 7 \cdot 7$)

Figure 18

"Cocklebur" ($2n + 11 \cdot 12$) "Wedge" ($2n + 11 \cdot 11$)

Figure 19

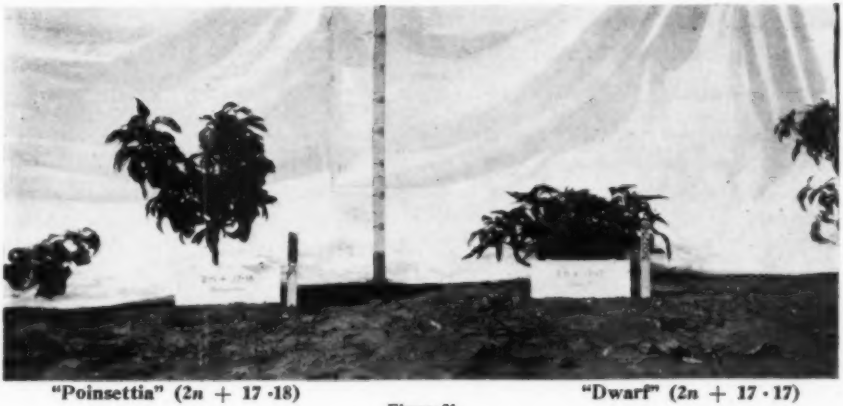
PRIMARY AND SECONDARY MUTANTS

"Resemblance with a difference" may be said to characterize the primary forms and their respective secondaries. Since each has an extra chromosome, such forms do not breed true.

PRIMARIES SECONDARIES

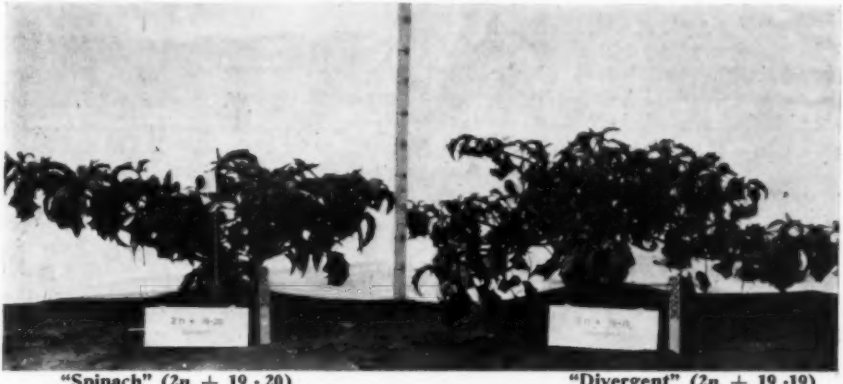
"Reduced" (2*n* + 15 · 16) "Scalloped" (2*n* + 15 · 15)

Figure 20



"Poinsettia" (2*n* + 17 · 18) "Dwarf" (2*n* + 17 · 17)

Figure 21

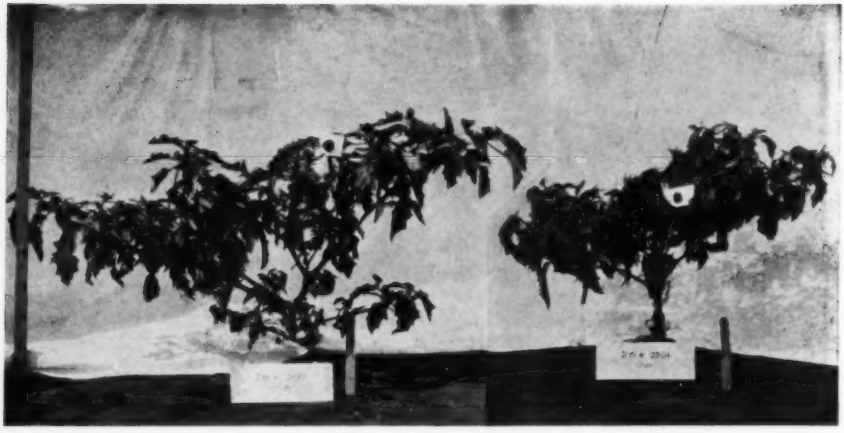


"Spinach" (2*n* + 19 · 20) "Divergent" (2*n* + 19 · 19)

Figure 22

PRIMARY AND SECONDARY MUTANTS

The increased "concentration" of the genes in each chromosome or half chromosome that is extra in each of these mutants produces a progressive intensification of the characters transmitted by the extra chromosome.



PRIMARIES OF THE SMALLEST CHROMOSOMES

Figure 23

No secondaries of these mutants have yet been found. "Globe," on the left, was the first of the chromosomal mutants to be discovered and has been known since 1915. It has the 21·22 chromosome extra. "Ilex," on the right, is the $2n + 23 \cdot 24$ type.

Figures 13 to 23 show the primary and secondary $2n + 1$ types as they were growing in our demonstration garden plot this last summer. The habits of growth of the different plants, as well as the appearance of their capsules, show the wide differences in the effects of the hereditary pills from different chromosomes. There seems to be in general little similarity between the pills in the two different halves of a single chromosome.

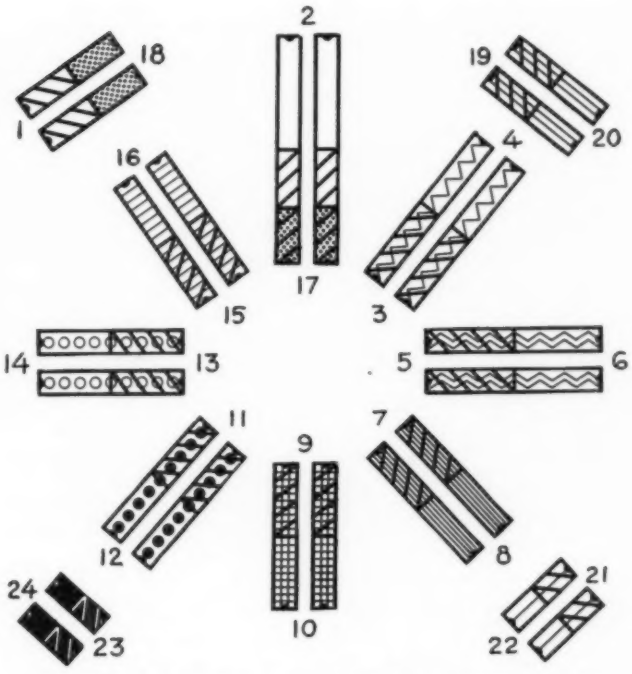
In addition to the factors already discussed in the two halves of the 1·2 chromosome, it will be seen from Figure 13 that the ·1 half contains factors tending to make the plant erect while the ·2 half contains factors that tend to make the plant spreading. The primary $2n + 1 \cdot 2$ plant is again intermediate in respect to erectness and spreading. In a similar way it will be seen from Figure 11 and Figure 14 that the ·5 half chromosome contains factors for erect habit, dark stem, small, short capsules, and narrow leaves while the ·6 half contains factors for spreading habit, light stem, long capsules and broad leaves. The primary $2n + 5 \cdot 6$ is intermediate in respect to these characters of its two secondaries.

In Table I the primary and secondary types so far discovered are summarized. It has been our convention to give the odd number to the first secondary chromosome identified, so the left hand column labelled secondaries has more representatives than that of

TABLE I

PRIMARY, SECONDARY, and TERTIARY $2n+1$ Types in STANDARD LINE 1

Chromosome size class	Secondary chromosome	Primary chromosome	Secondary chromosome	Tertiary chromosome
L	1 · 1	1 · 2	2 · 2	2 · 9
1	3 · 3	3 · 4	-	4 · 6
1	5 · 5	5 · 6	6 · 6	4 · 5
M°	7 · 7	7 · 8^{0}	-	-
M°	9 · 9	9 · 10^{0}	$^{0}10 \cdot 10^{0}$	2 · 9
M°	11 · 11	11 · 12^{0}	-	-
M	13 · 13	13 · 14	14 · 14	10 · 13
M°	15 · 15	15 · 16^{0}	-	-
m	17 · 17	17 · 18	-	10 · 13
m°	19 · 19	19 · 20^{0}	-	-
m°	-	$^{0}21 \cdot 22$	-	-
s°	-	23 · 24^{0}	-	-



MODELS OF THE CHROMOSOMES OF THE *B*-RACE

Figure 24

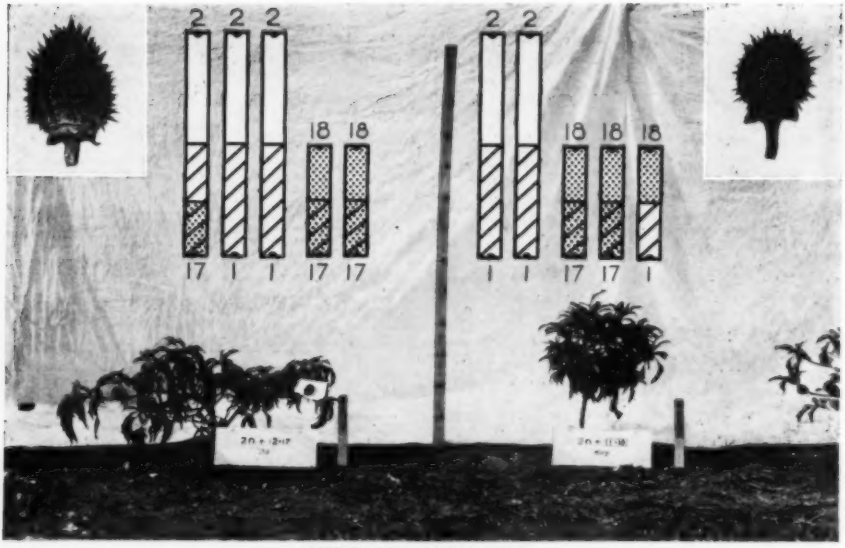
The chromosomes of this race are like those of the Standard Line 1 (Figure 5) except that parts of the 1·2 and 17·18 chromosomes have "changed partners" by segmental interchange. The resulting new 1·18 and 2·17 chromosomes have the same gene-complement as Line 1, but the gene-pills are in different bottles. The two races are alike in outward appearance; the difference between them appears when they are crossed, for in the progeny of such a cross characteristic chromosomal abnormalities occur.

the complementary secondaries to the right. It will be noted that for four primaries we have discovered both the secondaries and that for only two primaries (those with the smallest two chromosomes extra) do we fail to have at least a single secondary.

Tertiary Types

In the last column of the table are listed a few $2n + 1$ types which have appeared in our cultures in which the extra chromosome is made up of parts of two different chromosomes. Such plants have been called *tertiary* $2n + 1$ types.

Tertiary types form an interesting example of the value of attacking a problem from different points of view. The first clue came from the breeding behavior. Purple and white flowers we found to be inherited, according to Mendel's law, as others had found before us. By the method of trisomic ratios, the factors for flower color were determined to be in the 17·18 chromosome. The ratios of purple and white flowered individuals in the offspring were as expected, except when certain races were used in the crosses. Such abnormal races were called *B* races in distinction from the *A* races which behaved normally in inheritance, and by several breeding methods it was found possible to classi-



TERTIARY MUTANTS

Figure 25

Two mutant forms produced by crossing the *B* race (Figure 24) with Line 1 (Figure 5). On account of the differences in the distribution of the hereditary pills in the chromosome bottles, forms are obtained by this cross which have extra "tertiary" chromosomes made up of parts of two non-homologous chromosomes. In this they differ from the forms having as extra material, an entire chromosome, (primaries), or the doubled half of one chromosome (secondaries).

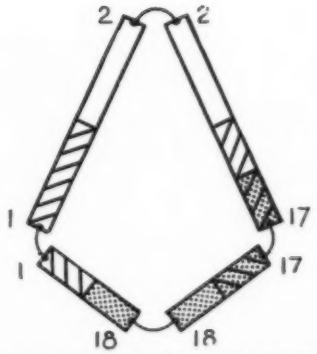
fy the races in our collection into *B's* and *A's*. Later two types were discovered each with an extra chromosome which appeared only in offspring from parents hybrid for an *A* and a *B* race.

One of them called "Wiry" resembled in some respects the little $2n + 1{\cdot}1$ plant which we have shown in Figures 10 and 13. In other respects it resembled what we should expect a $2n + 18{\cdot}18$ plant to look like if it should be discovered. The other type resembled both the $2n + 2{\cdot}2$ type of Figure 10 which was called "Sugarloaf" and at the same time resembled the $2n + 17{\cdot}17$ type which was called "Dwarf." In fact we gave this type the name of "Dwarf-Sugarloaf" before its chromosome constitution was understood.

A study of the connections of chromosomes in "Wiry" gave Belling the final explanation of this type from which he was able to develop the hypothesis of segmental interchange. In brief, the hypothesis supposes that in the origin of *B* from *A* races, parts of the white or 1·2 chromosome have interchanged segments with the stippled or 17·18 chromosome to give the chromosomal constitution shown in Figure 24.

Figure 5 which represents an *A* race differs from Figure 24 only in the different distribution of the white and stippled material. There are the same hereditary pills in each but in the *B* race the stippled pills are in two kinds of bottles whereas in the *A* race the same stippled pills are in only one kind of bottle. The *A* and *B* races may look alike, therefore, in external appearance. What the factors are in the modified *B* chromosomes may be judged from the effects which they produce when present as extras.

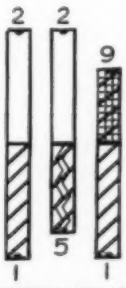
In Figure 25 are shown habit photo-



CHROMOSOME RINGS CHARACTERIZE HYBRIDS BETWEEN CERTAIN RACES

Figure 26

When Line 1 and the *B* race were crossed, the hybrid showed circles of four chromosomes under the microscope. On the principle that the like ends of chromosomes attract each other, Belling proposed the theory of segmental interchange which explains the phenomena observed in these hybrids. This theory has furnished an explanation for the circles of four and more chromosomes regularly found in many of the species of Oenothera and in certain other plants.



A COMPENSATING TYPE

Figure 27

Models of chromosomes in compensating type "Nubbin." Only one intact 1·2 chromosome is present. The chromosomes 1·9 and 2·5 "compensate" to form the equivalent of the missing 1·2 chromosome, leaving the ·9 and ·5 halves as excess material to influence the development of the plant.

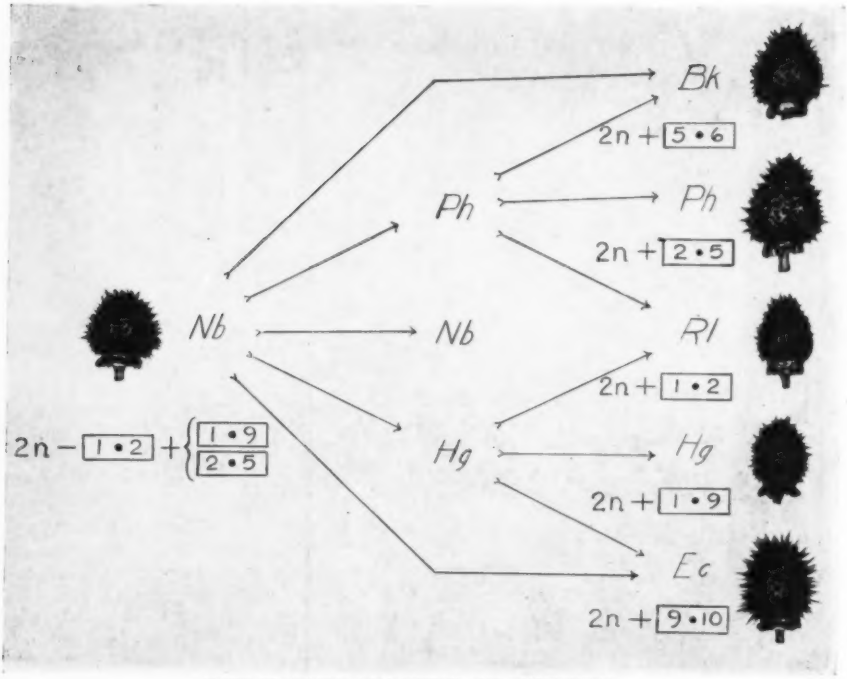
graphs together with capsules and chromosome models of the two tertiaries, Wiry $(2n+1\cdot18)$ and Dwarf-Sugarloaf $(2n+2\cdot17)$. A complete knowledge of the factors in the different parts of the 1·2 and the 17·18 chromosomes might have enabled us to calculate exactly how much of each of them was present in the extra chromosome of these tertiaries, even without the tests afforded by microscopic examination.

Prime Types

The hypothesis of segmental interchange as an explanation of *B* races and the two tertiaries obtained from them has been confirmed by a number of independent lines of evidence. Among these is the attachment of chromosomes in hybrids. If we cross a *B* race, the chromosomal diagram of which is shown in Figure 24, with our standard Line 1, shown in Figure 5, a hybrid will be formed in which all the chromosomes will be attached in pairs at the reduction division except the four chromosomes that contain the white and the stippled material. These four chromosomes will form a circle of four, since the like ends are attached as shown in the models in Figure 26.

This method of testing races in nature by crossing them with our standard Line 1 was used with about 550 different races obtained from widely separated regions of the world. A study of the chromosome connections in these hybrids made by Dr. Bergner and Miss Satin has shown that there are at least four types of the Jimson Weed in nature which have interchanged chromosomes. These chromosomal races have been called Prime Types.

The first is our standard Line 1, which is Prime Type 1 or more simply, PT 1. The next is the *B* race or PT 2, which is the most common race in Europe. The third, PT 3, is the only race in Peru and possesses the modified chromosomes 11·21 and 12·22 formed by interchange of the 11·12 and 21·22 chromosomes of our standard Line 1. The fourth prime type is PT 4, first found in Jamestown, Virginia, which place is the origin of the name Jamestown Weed, later abbreviated to Jimson Weed. It has the interchanged chromosomes 3·21 and 4·22. The re-



THE VARIED PROGENY OF "NUBBIN"

Figure 28

The compensating type "Nubbin" has the parts of a missing 1·2 chromosome combined with extra material (·9 and ·5) to form two new chromosomes. This peculiar situation results in a variety of types in the next generation. These carry either an extra complete chromosome, or extra tertiary chromosomes of the types shown. Without an understanding of the chromosomal situation the phenomena here observed would appear to be an exception to Mendelian inheritance.

maining prime type of the Jimson Weed found in nature (PT 7) has chromosomes modified by exchange of the terminal humps on the 9·10° and the 19·20° chromosomes.

These prime types found in nature may be compared in a way to incipient species, since it has been found that all the species so far tested differ one from the other in respect to certain of their chromosomes which appear to have interchanged segments. It will not be possible in the time at our disposal to discuss the chromosomal differences between species but it will be evident that we are accumulating a collection of different kinds of modified chromosomes from nature both from the prime types within the Jimson Weed and also from other species.

TABLE II

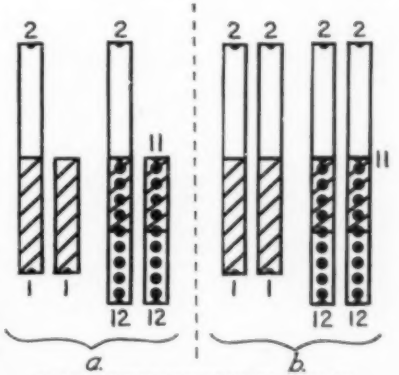
PRIME TYPES IN NATURA

PT	x L1	L1 chromosomes involved	Pollen abortion in F_1	Modified chromosomes	First pedigree	Origin
1	BV		OK		L1, S.I.1	Nature
2	♂ 4	L-1·2 m-17·18	OK	L-2·17 m-1·18	"B",S.I. 4	Nature
3	♂ 4	M-11·12 S-21·22	± 25%	M-11·21 S-12·22	S.I. 224	Nature
4	♂ 4	L-2·4 S-21·22	OK	L-4·22 S-2·21	S.I. 442	Nature
5	Tr.4	L-1·2 M-11·12	OK	L-12·11·2	27277(1)	Radium
6	Tr.4	L-1·2 M-11·12	OK	L-12·11·2 m- ·1	27277(1)	Radium
7	♀ 4	$M\text{-}9\cdot10^{10}$ $m\text{-}19\cdot20^{20}$	± 80%	$M\text{-}9\cdot10^{20}$ $m\text{-}19\cdot20^{10}$	S.I. 7	Nature
8	♀ 4	$M\text{-}9\cdot10^{10}$ $M\text{-}11\cdot12^{12}$	± 80%	$M\text{-}9\cdot10^{12}$ $M\text{-}11\cdot12^{10}$	270316(100)	Radium
9	Tr.4	m-19·20 s-23·24	± 25%	M-20·19·25 s- ·24	261294(?)	X-ray
10	♂ 4	L-1·2 M-13·14	OK	L-1·13 1-2·14	261294(?)	X-ray
11	♂ 4	M-11·12 M-13·14 m-17·18	± 25%	L-12·17 M-11·13 s-14·18	270316(270)	Radium
12	♂ 4	M-13·14 s-23·24	OK	M-13·23 s-14·24	27277(1)	Radium
13	♂ 4	L-1·2 M-9·10	OK	L-1·9 M-2·10	261031(?)	Radium

GENE-PILLS IN NEW BOTTLES

Figure 29

Compensating type in which compensation is between a secondary 1·1 and a tertiary 2·17 "*B*" chromosome, leaving the ·1 and ·17 halves as excess material to influence the appearance of the plant.



NEW CHROMOSOMES FROM RADIUM-TREATMENT

Figure 30

Models of chromosomes altered by radium treatment. (*a*) At left, result of breaking the 1·2 chromosome and attaching the ·2 half to the 11·12 chromosome. (*b*) At right, pure-breeding type with extra ·2 material in double dose, derived from *a*. See also Figures 33 and 34.

An especially fruitful source of new kinds of chromosomes comes from the treatment with X-rays and radium, which stimulates breakage and interchange of segments of chromosomes. From radiation and natural sources we now have isolated over 80 prime type races and have found many more which are waiting to be purified.

Table II lists only 13 of these prime types and shows not only the modified chromosomes but also the standard chromosomes of Line 1 from which they were derived and configurations of these chromosomes in hybrids with Line 1. Our extensive collection of prime types, only a few of which are shown in Table II, together with the primary, secondary, and tertiary $2n + 1$ types from Table I, are a source of different kinds of chromosomes which correspond to a printer's font from which he selects the individual letters for any desired word.

Compensating Types

How we have used our font of chromosomes may be seen from a few examples. Let us start with the models of Figure 5 and take away one of the two large white or 1·2 chromosomes. We will keep the other white chromosome and add to it two new chromosomes each with some white material as shown in Figure 27. Between them, the two new chromosomes make up the equivalent of the whole white chromosome that was taken away.

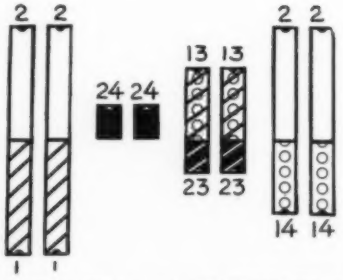
In more technical language we may say that the ·1 half of the 1·9 and the ·2 half of the 2·5 chromosome together compensate to make the equivalent of the missing entire 1·2 chromosome. Figure 27 represents the chromosomal constitution of the compensating type "Nubbin" (*Nb*). It will be noted that in addition to compensating for the missing 1·2 chromosome, the two new chromosomes bring in extra chromosomal material in the form of a ·5 half and a ·9 half. This extra material has an influence upon the appearance of the plant as shown by the *Nb* capsule in Figure 28.

This photograph shows capsules also of the $2n + 1$ types thrown by *Nb* which include the new tertiaries, $2n + 1{\cdot}9$ and $2n + 2{\cdot}5$. The peculiarities of these two new tertiaries, as well as those of the compensating type *Nb*. are what might be expected if their modi-

PAIRED NEW CHROMOSOMES PRODUCE A PURE-BREEDING TYPE

Figure 31

Models of chromosomes of a second pure-breeding type. There is no 1·2 chromosome although all the genes are present. See also Figures 33 and 34.



A NEW DEAL IN CHROMOSOME BOTTLES

Figure 32

Models of chromosomes of a third true-breeding type produced by taking chromosomes from three prime types (PT's 9, 10, and 12). These new bottles have a complete set of gene pills, and the equivalent of a 2·2 chromosome left over. The form is similar to the secondary $2n + 2{\cdot}2$ mutants (shown in Figures 10, 11, and 13) which have a 2·2 chromosome extra.

fied chromosomes were made up as indicated in the models. As a matter of fact, the peculiarities of appearance and breeding behavior gave the clue to the composition of the chromosomes which was found to check with the behavior of the chromosomes as observed under the microscope.

Figure 29 shows a compensating type in which the compensation is between the secondary 1·1 chromosome and the long 2·17 tertiary chromosome from the *B* race. A ·1 half from the 1·1 chromosome compensates with the ·2 half from the 2·17 chromosome, leaving as extra material a ·1 half, a ·17 half and the inner portion of a ·1 half. The plant gets its relatively erect habit of growth and narrow leaves from the extra ·1 half (cf. the $2n + 1{\cdot}1$ plant at right in Figure 13) and its drooping leaves from the ·17 half (cf. the $2n + 17{\cdot}17$ Dwarf plant in Figure 21).

These two examples will suffice to show how compensating types are made up and how they give information about the hereditary pills in the material which is left over after the missing chromosome has been compensated. They are also of use in locating pills in a particular hereditary bottle to which they belong by methods which we cannot discuss here. We are fortunate, therefore, in having at least one compensating type for each of the 12 chromosomes except three, and crosses are being made which we hope before long will produce compensating types also for these last three chromosomes.

Pure-Breeding Extra-Chromosomal Types

The primary, secondary, and tertiary types that we have been discussing form a varied collection of plants which differ from one another by groups of factors due to the extra chromosomal material which they contain. In this respect they resemble distinct species but they cannot be called species because they do not breed true by seed. If we wish to propagate them we must use vegetative methods such as cuttings and grafts, as is done for certain extra-chromosomal types of fruits. Recently, however, methods have been devised which make it possible in certain cases to synthesize pure-breeding types with extra chromosomal material. Our efforts in this direction have been concentrated on the largest or 1·2 chromosome, more especially on the ·2 half of this chromosome.

The first pure-breeding type has been purified and listed in Table II as PT 5. As the result of radium treatment the 1·2 chromosome was broken into two halves. The ·2 half was permanently united to the ·11 end of the

SYNTHETIC "NEW SPECIES"

Figure 33

Morphologically these types are strikingly similar even though their chromosomes are different. Each has material equivalent to a 2·2 chromosome extra. Their chromosomal models are shown in Figures 31 and 32. They are more different from the form from which they arose than some of the described species in Datura. The quotation marks around the words "New Species" are in deference to taxonomists some of whom would confine their concept of species to forms which have arisen in nature and would exclude from the term these pure-breeding types which have been made up to specifications from a knowledge of the different parts of the chromosomes involved.

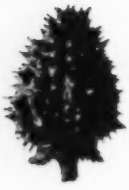
11·12 chromosome leaving the ·1 half as a free fragment. Models of these chromosomes in the affected plant are shown in Figure 30*a*. There is no extra material. By proper breeding procedure, however, the ·1 fragment was eliminated as also the normal 11·12 chromosome. The 11·12 chromosome with the attached ·2 half was doubled and the 1·2 chromosome was returned to the paired condition as shown in Figure 30*b*. A plant was thus formed with the ·2 extra half in double dose. The form is indistinguishable in appearance from the secondary $2n+2{\cdot}2$ type shown in Figures 10, 11 and 13 which also has in excess a double dose of the same half chromosome.

The second pure-breeding type was synthesized by combining the ·1 fragment shown in Figure 30*a* with the secondary 2·2 chromosome. In the process both the 1·2 chromosomes were eliminated and a plant formed with the chromosomes shown in Figure 31. Each ·1 fragment compensates with one half of a 2·2 chromosome, leaving a ·2 half extra. There will be, therefore, two ·2 halves as total excess material. In consequence the type is indistinguishable in appearance from the previously discussed pure-breeding type which also has two extra ·2 halves. It breeds essentially true except that it occasionally throws a weak seedling with three instead of two ·1 fragments. These latter are rare, however, and their offspring revert to the type in the next generation.

The third pure-breeding type was synthesized from three different prime types shown in Table II. In the race finally obtained, the 1·2 chromosomes were retained but both the two 13·14 and the two 23·24 chromosomes were eliminated. In their place two ·24 fragments were brought in from PT 9 which with two 13·23 chromosomes brought in from PT 12 compensated to form the equivalent of a pair of 23·24 chromosomes. The two ·13 portions left over together with the pair of 2·14 chromosomes taken from PT 10 formed the equivalent of a pair of 13·14 chromosomes. As a final result, shown by models in Figure 32, there were left over the two ·2 halves. This extra material brought about changes in the appearance of the plant similar to those produced by the two extra doses of the ·2 half in the pure-breeding types previously discussed. Plants of the first two of these synthesized types are shown in Figure 33.

2n STANDARD

24 CHROMOSOMES
BREEDS TRUE



$2n + [2 \cdot 2]$

25 CHROMOSOMES
CANNOT BREED TRUE

$2n - [11 \cdot 12]_2 + [2 \cdot 11 \cdot 12]_2$

24 CHROMOSOMES
BREEDS TRUE

$2n - [1 \cdot 2]_2 + \left\{ \begin{matrix} [1\ ]_2 \\ [2 \cdot 2]_2 \end{matrix} \right.$

26 CHROMOSOMES
BREEDS TRUE

$2n - \left\{ \begin{matrix} [13 \cdot 14]_2 \\ [23 \cdot 24]_2 \end{matrix} \right\} + \left\{ \begin{matrix} [2 \cdot 14]_2\ [24]_2 \\ [13 \cdot 23]_2 \end{matrix} \right.$

26 CHROMOSOMES
BREEDS TRUE

TRUE-BREEDING EXTRA CHROMOSOMAL TYPES

Figure 34

Above is shown a capsule of the normal Jimson Weed, and below it at the left that of the 25-chromosome secondary "Sugarloaf." The three true-breeding synthetic "species" all have an extra double dose of ·2 chromosomal material so that they are essentially true-breeding "Sugarloafs."

Capsules of all three are shown in Figure 34, together with a capsule of a secondary $2n + 2 \cdot 2$ type and of a normal $2n$ for comparison. The capsules with extra ·2 material all show the characteristic sugarloaf shape.

There are two prerequisites for success in synthesizing pure-breeding types with extra chromosomal material. First, the extra material must be capable of being transmitted through the pollen, as well as through the egg cell, in order to get a double dose in the offspring. This is not enough, as we discovered in the case of the type with 2 extra 21·22 chromosomes shown in Figure 8. Every pollen grain and ovule must have each of the 12 chromosomes and every part of these chromosomes is apparently necessary for their functioning. The second prerequisite, therefore, is that the extra material must be attached to a necessary part of a chromosome.

It will be noticed from the legends to the capsules in Figure 34, that in one of these pure breeding types we have 24 chromosomes—the same number as in the normals, but in the other two we have 26 chromosomes—two more than normal.

Artificial New Species

The pure-breeding types are more distinct from the original form from which they arose than some of the species of Datura which have been founded on single factor differences. Our types we have ventured to call artificial or synthesized "new species." They differ from the ancestral form not by a single factor but by a whole group of factors. Their greatest difference from species in nature appears to lie chiefly in the fact that we know their method of origin, having made them up to specifications, as it were, from a knowledge of the different parts of the chromosomes involved. Whether nature has used such methods, we do not yet know. But it should be remembered that often, when man has devised a method which he has thought unique, nature has been found to have had the priority in the use of the same method.

Table III is an incomplete summary of the extra chromosomal types that have been identified in the Jimson Weed, together with the number theoretically possible on the assumption that any break which occurs takes place in the middle of the chromosome. This is known not to be the case however, so that the number theoretically possible is usually larger than that given. There are over 150 forms that have been identified. This number could be increased greatly by isolating the tertiary $2n + 1$ types from our collection of prime types.

It has been possible in the space available to me to tell only a little about the pieces in our game of domino chromosomes. I hope it has been obvious that our actual purpose has been to learn how nature has played her game with real chromosomes. In this we believe our joint undertaking has made some progress with a single plant. In the study of a major biological problem like that of evolution, progress will be most rapid we believe, if the problem can be stated in terms of its most vital

TABLE III

SUMMARY OF CHROMOSOMAL TYPES IN DATURA STRAMONIUM

I=Primary (unmodified) chromosomes. II=Secondary chromosomes (with two like ends). III=Tertiary chromosome (with ends from two different primaries).

Chromosomal types	No. forms identified	No. forms theoretically possible	Formulae
1n, 2n, 3n, 4n	4	4	
1n + I	1	12	n
1n + II	1	24	2n
2n + I	12	12	n
2n + II	24	24	2n
2n + III	13	264	2n(n-1)
2n + 2 I	0	12	n
2n + 2(I & II)	1	24	2n(Ia:II related)
$2n + I + I$	47	66	$\frac{n(n-1)}{2}$
2n + I + II	2	264	2n(n-1)(Ia:II unrel.)
2n + I + III	0	3168	2n^2(n-1)
$2n + I + I + I$	1	220	$\frac{n(n-1)(n-2)}{6}$
2n - I	2	12	n
2n + II - I	1	24	2n(Ia:II related)
2n - I + II + III	7	264*	2n(n-1)
2n - I + III + III	12	264*	2n(n-1)
2n - I + III + III + I	8	3168	2n^2(n-1)
2n + 1 free fragment	7	24	2n
2n + 2 free fragments	4	24	2n
2n + 1 trans. frag.	1	24**	2n
2n + 2 trans. frgs.	1	24**	2n
3n + I	1	12	n
3n - I	1	12	n
4n + I	2	12	n
4n + 2 I	1	12	n
4n + 3 I	1	12	n
4n - 1	0	12	n
$4n + I + I$	1	66	$\frac{n(n-1)}{2}$
4n + I - I	1	132	n(n-1)
4n - I - I	1	66	$\frac{n(n-1)}{2}$
$4n + I + I - I - I$	1	2970	$\frac{n(n-1)(n-2)(n-3)}{4}$

*264 morphological types, but 3168 different chromosomal types, if the parts of chromosomes which have interchanged are considered. **24= morphological types, but 576 different chromosomal types if ends to which fragments are translocated are considered. Calculations above assume that the two parts into which a chromosome breaks are always equal. Hence the figures given form a minimum.

elements, and if use can be made of the experimental method. With the Jimson Weed we are attempting to think in terms of the evolution of chromosomes and are subjecting our hypotheses to experimental tests from different points of view. We trust that the studies on the humble Jimson Weed will contribute in some small measure to an understanding of how life has become what it is, and what it is still becoming.

Genetics Applied to Man

GENETIC PRINCIPLES IN MEDICAL AND SOCIAL SCIENCE, *by* LANCELOT HOGBEN. 230 pp. Williams and Norgate, London. 1931.

THIS book by the Professor of Social Biology at the University of London does not aim to be a comprehensive treatise on human inheritance, but rather to re-examine critically some of the materials of human genetics which have been accumulated by numerous investigators, and to apply the modern quantitative treatment developed in experimental animal genetics.

The first chapter is of interest both to medical scientists and sociologists. Chapters II and III present abundant clinical material which appeals directly to the interests of the workers in human pathology and preventive medicine. The last five chapters are full of facts and challenging ideas for social biologists, social psychologists, and ethnologists.

The eight chapters, each one practically complete in itself, are: I, Problem of twin resemblance; II, Single gene substitutions in human pathology; III, Seriological data for the study of gene localization; IV, Genetic basis of social behavior; V, Concept of race; VI, Nature of genetic selection in the social group; VII, Growth of human populations; VIII, Social application of genetic principles.

This book is for readers who are already quite familiar with the general principles of genetics. One who casually turns the pages and notices numerous tables and mathematical statements scattered throughout the text may get the impression that it is a very technical book for statisticians and mathematicians. The truth is that Professor Hogben has assumed that the reader has a general acquaintance with the elementary principles of correlation, statistics, algebraic probability, and the simpler methods of mathematical analyses. However a large proportion of the pages of the book may be read easily by students of heredity who have had no special training in mathematics and statistics.

This book makes a decided contribution to genetic science in that it suggests numerous lines of needed research and sets forth certain methods which the human geneticists may follow profitably.

MAURICE A. BIGELOW.
Columbia University.

FACT AND SPECULATION IN THE STUDY OF EVOLUTION

A Review

THE SCIENTIFIC BASIS OF EVOLUTION, *by* THOMAS HUNT MORGAN, Director of Kerckoff Laboratories, California Institute of Technology. Price, $3.50. New York, W. W. Norton & Co. 1932.

THE books that Professor T. H. Morgan has written during the last twenty years not only indicate the mode and the direction of his own intellectual development, but in addition they have served as milestones on the road along which the science of genetics has travelled. Each in its turn has marked a place where the author has rested awhile, looked back to find satisfaction in the progress made, looked forward in enjoyment of anticipation of even more exciting things yet to be encountered.

In the earlier days, whilst the chromosome hypothesis in its simplest form was being developed, the road stretched forward across a level, fertile plain, straight to a far-distant horizon, but latterly, as the result of the impact of the newer cytology and biometry, the way has become tortuous, passing in and out amongst hills crowned with shading trees and winding along valleys in which the voice of water insistently invites the fatigued experimentalist to turn aside and idly cultivate a philosphy. Cytology, developmental physiology, biometrics, biological philosophy, each of these, rather removed from the hard, high road of disciplined genetical experimentation, has its own allure. Shall we who lag so far behind seek novelty, adventure, serenity, in the groves of cytology; shall we leave the gene behind us, a captured, tortured thing, and ponder over the larger problems of evolution; shall we, exhilerated by our triumphs over Drosophila and maize, attempt the the task of re-fashioning man and of re-moulding society? To us, invigorated by the journey, surely this would be a mere bagatelle. We have travelled far and fast, and there is no difficulty that we feel we could not overcome. Let us ask Morgan what he thinks, for he has journeyed from the very beginning, and, knowing every inch of the road so far, surely he must know whither it leads.

Professor Morgan has never been so engrossed in the mapping of the chromosomes as to forget for one moment that the great promise of genetics has always been that it would in time make a notable contribution to evolution theory. Time and time again he has returned to this theme. His mind is a vast store of verifiable fact derived from experimentation that has always prevented him accepting at all easily the generalities of the philosophers.

The Nature of Mutations

To the author, the central problem of evolution still remains the origin of mutations, and the subsequent operation of natural selection on a genetically diverse population is regarded as being of secondary interest, however important it may be in applied genetics. Since the causes of mutation are only at present guessed at, Morgan, the skeptic, declines to commit himself to the proposition that mutations are necessarily without direction. Our present lack of knowledge concerning this matter provides free scope for the speculations of the metaphysician, and in this book Morgan, the mechanist, smites Smuts, Haldane, Whitehead and the rest; a delightful joist and as we drag the fallen from the lists we agree with the author that his opponents really had no contribution to offer that would help us in our workaday business of biological research. With him we say that we will not depart from the meth-

ods of analysis that have served biological science so well in recent years.

Human Genetics

We know by now that Professor Morgan has a very low opinion of the human subject as genetical material, and also that he has always reacted very strongly indeed to the crudities and anecdotalism of those who have written so easily of the apparent simplicities of the modes of inheritance of the most complicated human attributes. In this book references to human genetics are for the most part casual asides, and have very little bearing on the main theme; but surely he is mistaken when he states that only a few strictly dominant mutational changes are known in man. Actually a list of such running into three figures could be compiled.

Professor Morgan, whose views on this matter will be shared by many who have suffered at the hands of Sewall Wright, Fisher, Haldane, Hogben and the rest of the biometricians, seems to think that their methods are inferior to the usual ones employed in genetical experimentation, but grants that they may possess a certain value in studying such problems as complex racial differences. Had I said this, I should have known that it was because my mathematical equipment is exceedingly meager. After all, the study of human genetics is nothing but an assay in applied genetics, and all that can be attempted is the working out of problems that are to be compared with those of the earlier and simpler days of Mendelism. The inherent difficulties of human material are such that complex and rather roundabout methods simply have to be devised and employed, but these, in the hands of the statistically competent, can and do produce results which are as significant as are the ratios which one can obtain by controlled experimentation.

By the way, there is a trifling error in the section dealing with the blood groups. Surely what is important in blood transfusion is that the serum of the recipient should not agglutinate the corpuscles of the donor.

That genetics has its contribution to make to evolution theory has been demonstrated. Quite recently there appeared an excellent book on this particular topic which might have been called "The Effects of J. B. S. Haldane" but which was actually entitled "The Causes of Evolution." Those who read and enjoyed this should now read this book of Morgan's, for, whilst both are very worth while contributions to the subject, the difference between them, reflecting differences in the approach and attitude of the respective authors, is illuminating. This latest book of Professor Morgan's is strongly recommended to everyone interested in genetics, and particularly in the bearing of genetics on evolution. Even the professional geneticist will find it profitable to read this simple account, written by a master of exposition, in which the salient features of recent cytological and genetical work relating to the chromosome theory of organic inheritance are so skillfully selected and presented.

F. A. E. Crew.

University of Edinburgh

VI International Botanical Congress

THE Organizing Committee of the VI International Botanical Congress from various sides has been asked to change the dates of this Congress; the Committee has now decided that the Congress will meet at Amsterdam (Holland), September 2-7, 1935.

A first notice regarding this Congress has been sent out to a number of addresses; for additional copies please apply to the secretary, Dr. M. J. Sirks, Wageningen, Holland.

DEFECTIVE SKULLS INHERITED IN SWINE

E. H. Hughes and Hugh Hart
University of California

DEFECTS and abnormalities have manifested themselves in all classes of domestic animals. Some are hereditary and are therefore of scientific interest as well as of economic importance. Hereditary characters that are lethal, partially lethal or semi-lethal in their effects should be reported. Livestock producers and others interested in animal improvement should be more fully informed of such defects. No one can estimate and few appreciate the annual losses accruing through hereditary lethal factors and defects.

Defects Previously Reported

Skull, ear and skin defects have been reported in a single Berkshire pig by Nordby.[6] Except for these defects, this pig seemed normal at ninety days of age. He exhibited a tuberosity located in the posterior area of the femoral fossa. Nordby[7,8] reports a defect which he terms a brain hernia on the front part of the forehead with a skull opening. This deformity has been under observation in five purebred herds of swine over a sufficient period of time to permit the defect to be recognized as hereditary. In a certain strain of Duroc Jersey hogs he has shown that shriveled or very small ears are not uncommon. In some cases there is no opening from the outer ear into the skull. These two conditions seem to be associated. The "Catlin Mark," an inherited defect in the parietal bones in man reported by Goldsmith[24] is also of interest in this connection.

Investigating hernia in swine, Warwick[13] found that 1.68 per cent of male pigs raised were affected with scrotal hernia and about 0.60 per cent with umbilical or navel hernia. Approximately 1.00 per cent of female swine were affected with hernia, most of which were umbilical. During three years' observation 4.19 per cent of the male pigs in the herd, from which the parents for the study of this character were selected, were herniated. In the first generation breeding for hernia, 14.28 per cent of the male pigs were herniated and in the second generation 42.00 per cent of the male pigs were similarly affected.

Warren and Atkesen[12] report an unusually large number of male calves with umbilical hernia that appeared in two herds in which the same sire had been used. In three herds 21 herniated animals, the descendants of one common ancestor, were observed. They suggest that the defect is sex-linked.

Congenital cataract in cattle has been studied by Detlefson and Yapp.[2] An attempt was made to fix the desirable economic characters of a Holstein-Friesian bull by inbreeding. This bull mated to unrelated cows produced 93 offspring of the F_1 generation. F_1 daughters when mated to an F_1 bull produced 63 F_2 calves, 55 of these were normal, and 8 showed well-defined congenital cataracts. They concluded that the cataract was evidently a recessive character and that the original bull was heterozygous for it.

Hadley[3] has studied congenital epithelial defects of calves in Wisconsin. He found certain characteristic lesions in grade and purebred Holstein-Friesian cattle. There was a defective skin formation below the knees and hocks, undeveloped claws, deformed ears and abnormalities of the muzzle, nostrils, tongue, hard palate and cheeks. The calves all died shortly after birth because they were not able to survive the infection which was acquired through the affected areas soon after birth. The author believes the factor for the defect is recessive.

Wriedt[15] describes two lethal factors and how they were distributed very widely in a well-known breed of cattle. Two of the best-known sires transmitted lethal factors to their progeny.

One bull (Gallus) transmitted a recessive lethal factor which, in double dose, produced calves without legs (amputated). The upper jaw was bent and almost all of the lower jaw was wanting. The other bull (Prince Adolph) transmitted a lethal factor for hairless calves. They died immediately after birth. As a direct result of the dissemination of the offspring of these great sires, amputated and hairless calves are sure to segregate. On one farm alone 16 amputated calves were born and in all districts of Sweden, where Holstein-Friesian cattle are common, the segregation of amputated calves has been noted. The character for hairless calves is also widespread in the breed. On one farm three sires were purchased and used one after another and each proved to be heterozygous for this lethal factor.

The same author states that it was impossible to maintain the unusual breed of white horses in the Fredericksborg stud. The suggested causes were a (lethal) genetic factor which killed the fetus, or a genetic factor for infertility when the white horses were mated together.

Crew[1] suggests that the condition which results in bull-dog fetal calves is caused by improper functioning of the pituitary and has a genetic basis.

Experiments conducted by Lush, Jones and Dameron[4] have shown that many cases of cryptorchidism in goats are inherited. The exact manner of the inheritance of this character has not yet been discovered.

A hereditary lethal deformity in new-born lambs has been reported and described by Roberts.[11] The character is not sex limited and is fatal at or before birth in most cases.

Out of 40 lambs only one was born alive and it lived only three days. The legs of the affected lambs are perfectly rigid so that it was impossible to bend them at the joints without breaking. The front legs are nearly always affected and may be fixed in almost any position. The condition is probably the result of a single recessive Mendelian factor coming from both parents.

Wriedt[15] has reported other abnormalities such as short eared and earless sheep, excessively short legs in sheep; bleeders among certain families of thoroughbred horses; dogs with eyes which are usually blue, with crooked pupils and sometimes so abnormally small that the dogs are blind.

Hairlessness in swine has been reported by Roberts and Carroll.[10]

Warwick[14] describes a condition in pigs at the Ohio and Wisconsin Experiment Stations somewhat simulating string halt in horses. In severe cases the pigs have difficulty in walking. The condition was found among experimental pigs fed a wide range of rations. In the same publication cryptorchids or ridglings and entropion or turned-in eyelids in sheep and lambs are reported.

Cryptorchidism and its importance to swine producers and processors of pork products has recently been discussed by Nordby.[9] He reports that cryptorchidism is prevalent in swine and that it appears to be inherited.

McKenzie[5] found ten cryptorchids in a population of 107 pigs of both sexes. They were sired by one boar, and out of twelve different sows, which came from seven different litters out of five different sows. He concludes that cryptorchidism seems to be inherited.

Skull Defect in the California Experiment Station Herd

In 1929 attention was directed to skull defects in a Poland China herd in the San Joaquin Valley. Howarth* examined several specimens and found openings in the skulls similar to those reported by Nordby.[7] One specimen (Figure 35) exhibited a lack of contact between both the parietal and frontal bones where they join laterally. Many pigs in this herd had this defect, so many in fact as to constitute a serious economic menace. It was the first case reported to this station.

*Howarth, J. A., Calif. Exp. Sta., Davis, California.

Photograph courtesy of Dr. J. A. Howarth

DEFECTIVE SKULL

Figure 35

Skull of young pig showing opening. Both frontal and parietal bones are affected.

Recently four individuals affected with this deformity have been observed in the Poland China herd of the California Experiment Station. In these pigs there was lack of contact along the median line of the skull. All have been associated with the parietal bones. The openings have varied in length medially from 6 mm. to 16 mm. and in width laterally from 4 mm. to 6 mm.

Externally there is a protuberance located in the center of the forehead medially and laterally about midway between the top of the skull and a line drawn horizontally through the center of the eyes. The size of the mass protruding has varied, and the amount of the surface that is covered with hair varies in these individuals. The projecting part does not seem to be covered with a true outer epidermis but with a thick membrane. This condition agrees in part with Nordby's[6] report concerning ear, skin and skull defects in an individual Berkshire pig.

The affected pigs in this herd were as large or larger than their litter mates and just as strong. Two of the pigs, however, exhibited a lack of normal balance or equilibrium, especially while suckling. One individual died about five hours after birth. Another lived for a week after birth. In the latter case, whenever the protruding part received a blow or pressure the pig would fall, and make convulsive movements as though he had lost all sense of nervous control. This pig was killed by the herdsman during one of these spasms because he attacked his litter mates. A third pig, a litter mate of the one just described, grew and developed normally. The projecting part receded, the forehead became outwardly normal, except that no hair ever covered the center of the affected area. This pig was sold as a feeder to a neighbor, who marketed this individual weighing about 200 pounds at 8 months of age. The fourth pig lived for a period of about 7 weeks and seemed normal except for the skull defect. This individual was kept inside on concrete (his dam was on another experiment) and probably developed anemia. All the pigs in the litter became weak and died.

Record of the Ancestry

In the University herd, all the Poland China sows are descended from one purebred sow—Varsity Big Model 2nd, 826888. None of her offspring or their progeny ever exhibited the skull defect when mated to boars of various ancestry until an outstanding boar, Silverman A-59995, was purchased in 1929. The individuals described are the result of mating animals heterozygous for the factor. In this case they are inbred pigs. The matings in which the defects occurred are shown in Table I.

Silverman A59995 no doubt carried the factor for the defect, though he did not show it himself. He transmitted it to his offspring, and by inbreeding the deformity manifested itself in the second or succeeding generations. It seems certain this factor is hereditary and that Silverman A59995 was heterozygous for it. The character for the deformity is probably recessive and exhibits itself only when it comes from both the sire and dam.

Silverman, A-59995, mated to normal sows no doubt produced offspring some of which were normal and others heterozygous for the factor. As a result of such matings, no defective skulls were ever noted. Defective skulls have been found only as the result of mating Silverman, A-59995, to his daughters, or, in one case, a son of his mated to a granddaughter, all of which were probably heterozygous for the factor for defective skulls.

Of the four pigs showing the skull defect, only one finally went to market. However, in only one of the other three can it be said for certain that the defect proved to be lethal.

Silverman, A-59995, was an outstanding individual and sired the best hogs produced in the herd for many years. Being an individual of such merit, he was mated to his own daughters. By such mating, excellent individuals were produced. However, he apparently had at least one hidden characteristic of an undesirable nature which was also transmitted to his offspring, causing the condition discussed in this paper.

Altogether twenty matings were made in which Silverman A-59995, or two of his sons were mated to his daughters or granddaughters. From these matings 159 pigs were farrowed and only four defective skulls were noticed among them. However, as the size of the opening in the skull varied in its dimensions, it may be assumed that more pigs had the defect but the opening was so small as not to be noticed.

Nordby[7] postulates that this defect may in some way be associated as a causative agent in producing mummified pigs. The variations occurring in their development indicate death at different stages of pre-natal life. Since October, 1930, no cases of mummified pigs have been noted in our herd. The authors might hazard the view that mummified pigs are more closely associated with swine abortion than the condition discussed in this paper, which apparently is the same or similar to that discussed by Nordby.[7]

Importance of Hereditary Defects in Livestock

Hadley[3] has aptly said,"One of the aims of science is to keep accidents from happening." It is certainly far better economy to prevent defects than to attempt the difficult task of the eradication of physical abnormalities. Even though many deformities are not lethal in their effects, if the animals live and reproduce, the result is a multiplication of the number of undesirables.

Inbreeding has been a distinct aid to the geneticist and animal breeder in fixing desirable characteristics in the animals they have attempted to improve. Inbreeding concentrates the undesirable characters as well. It may therefore become an important aid in locating and eradicating semi-lethal and

TABLE I. Matings which produced swine with defective skulls.

Litter Number	Sire	Dam	No. of pigs in litter	No. of defective pigs
1	Silverman A59995	Daughter of Silverman A59995	9	1
2	Silverman A59995	Daughter of Silverman A59995	9	2
3	Boar 28 (Sire—Silverman A59995; Dam—Daughter of Silverman A59995)	Sow 22 (Sire—son of Silverman A59995; Dam—Daughter of Silverman A59995)	4	1

other undesirable hereditary characters.

A vast amount of information concerning nutritional deficiencies has been made available in recent years; the physiology of reproduction and factors affecting it are better understood than formerly; additional knowledge pertaining to immunity against disease is being obtained and disseminated, and recently there has come a realization that an accurate understanding of heredity can be of profound benefit to the producer.

The condition discussed specifically in this paper is probably widespread in occurrence. It is known to have existed in Wisconsin, Idaho, Oregon and California. Hereditary defects and abnormalities affecting various species of domestic animals have been reported as occurring in many countries of the world. It is certain that the operation of lethal and semi-lethal factors and other undesirable defects and abnormalities play a large part in the breeding of farm animals and are the source of considerable loss. Further research may result in a knowledge of the subject which will indicate greater losses than have yet been estimated.

Summary

1. Skull defects in swine, apparently hereditary, are discussed.

2. Defects of the skull as noted in this discussion may or may not be lethal in their effects.

3. Apparently the defect appears only when the offspring receives the recessive factor from both parents.

4. In the California Experiment Station herd this condition has manifested itself only among Poland China hogs.

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The Right to Be Well Born

Birth notice discovered by E. W. in the *Fountain Inn* (S. C.) *Tribune.*

Born, on Monday, January 27, to Mr. and Mrs. Jim Daderight, a son. The little fellow has the community's sincere sympathy. On his mother's side are three idiots and one jailbird of record, and nobody on the father's side of the house can count above four. With that start in life, he faces a world that will scorn and abuse and eventually hang him through no fault of his own.

Journal of the American Medical Association.

INHERITANCE OF SKIN DEFECTS

A Review

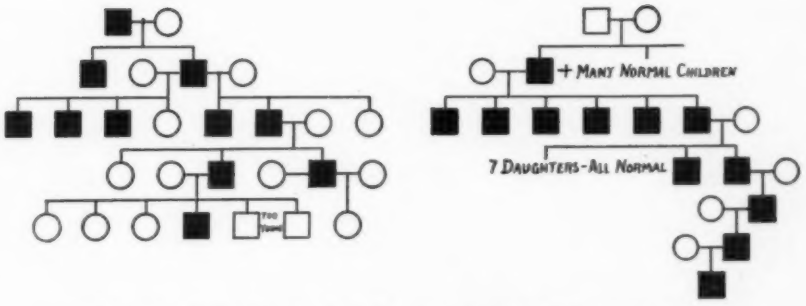
INHERITED ABNORMALITIES OF THE SKIN AND ITS APPENDAGES, *by* E. A. COCKAYNE. Pages X + 394, price $9.00. Oxford University Press, London, 1933.

THERE have been few attempts as yet at complete surveys of all material available in one particular field of human genetics. In fact, the "Treasury of Human Inheritance" and Waardenburg's splendid monograph concerning genetic characters of the human eye seem to be the only predecessors of Cockayne's book on inherited abnormalities of the skin and its appendages. Cockayne has collected in his treatise the available data concerning inherited abnormalities of the skin, teeth, hair and nails. This definition, however, is taken in the widest sense, so that many disorders are included which are not primary defects of the skin and its appendages although their most obvious defects are produced in these ectodermal structures, as for instance porphyrinuria.

A short description of the contents will give some idea of the multitude of genetic abnormalities covered by Cockayne. The introductory chapter gives a brief discussion of the general principles of genetics, obviously chiefly designed for the medical practitioner. The second chapter deals with "physiological abnormalities" (abnormalities of pattern, as piebald, white forelock, etc., and other abnormalities such as ringed hair, woolly hair, hypertrichosis of ears and eyebrows, freckles, mongolian blue spot). The third chapter is devoted to "metabolic errors" (albinism, lipomata, xeroderma pigmentosum, porphyrinuria, etc.). The fourth chapter reviews "errors of development of elastic tissue" (teleangiectases, cutis hyperelastica and epidermolysis bullosa). The fifth and sixth chapters deal with "dyskeratoses" (keratosis follicularis, monilethrix, porokeratosis, ichthyosis, etc.). The seventh chapter reports on "ectodermal dystrophies" (anidrotic ecotodermal dysplasia, alopecia, hypotrichosis, hypertrichosis, etc.). The eighth chapter deals with abnormalities of the teeth, and the ninth with abnormalities of the nails. The tenth chapter is entitled "disorders of growth," and includes a number of heterogeneous conditions (neurofibromatosis, naevi, epitheliomata, epidermoid cysts, etc.). Chapter eleven reviews "localized arrests of development" (e. g., aplasia cutis), "abiotrophies of elastic tissue," "unclassified anomalies of pigmentation," and "pigmentation due to endocrine disorders." The twelfth chapter records what little is known about abnormalities of the cilia, of branchial clefts, and of the breasts. Chapter thirteen reviews "conditions of doubtful aetiology" which probably are due both to genetic and environmental factors (seborrhea, vitiligo, alopecia areata, psoriasis, etc.). The fourteenth chapter deals with "vasomotor abnormalities" (cutaneous manifestations of allergy, angioneurotic oedema, etc.), and the last chapter records some dental anomalies associated with major disorders of development (cleido-cranial dysostosis, osteopsathyrosis, dwarfism).

Y-Chromosome Inheritance

It is impossible to give here a more detailed account of the many interesting conditions which are discussed by Cockayne, but we should like to direct attention to three case histories which, Cockayne thinks, suggest Y-chromosome inheritance. Tommasi has recorded a family with hypertrichosis of the ears. The persons showing this trait had a dense growth of hair on the whole anterior and the lower part of the posterior surface of the ears. The family tree which is reproduced here demonstrates that only the male members of the family showed this hypertrichosis of the ears. According to Cockayne "the pedigree strongly suggests that the gene was



POSSIBLE INSTANCES OF Y-CHROMOSOME INHERITANCE
Figure 36

Pedigree of a family in which the male members have hypertrichosis of the ears (growth of hair on the inner surface of the ears). The fact that the trait is inherited directly in the male line strongly suggests that the characteristic is determined by a gene located on the Y-chromosome—the male sex-chromosome.

A family in which fish scale skin (ichthyosis hystri gravior) is transmitted in the male line for five generations. Here again the inheritance of the trait follows that of the Y-chromosome.

in the Y-chromosome, but unfortunately Tommasi does not say whether the sons of the females were affected or not." The fact, however, that this hypertrichosis became apparent only at the age of 1 to 19 years seems to make it at least as probable that an autosomal gene was involved which for its expression depended on the internal secretion of the testes.

The second case to which Cockayne refers concerns the Lambert family, in which ichthyosis hystri gravior was transmitted to males only. In the abnormal individuals the whole body, except the face, palms and soles, was encased in a mass of excrescences of horny or semi-horny matter of a dusky brown color, in some places flat, in others prominent, rising half an inch above the skin at right angles to it, "so stiff and elastic that when ruffled by the finger the noise might have been heard at a considerable distance." The affected children were born with smooth skins and only became horny at two months.

The pedigree of this family, as given by Cockayne, is reproduced here. In the later generations, there were more children than is indicated in the pedigree, but according to the several authors who have studied this family every male was affected and no female. "It is most improbable that so many men, including scientists so eminent as Cuvier, Geoffroy St. Hilaire, and Tilesius, would be incorrect about a matter which evidently interested them greatly, and we may accept the fact that the males transmitted the abnormality to all their sons and to none of their daughters, while the daughters transmitted it to none of their children of either sex. The simplest explanation of this is to suppose that a dominant mutation occurred in the Y-chromosome of one of the germcells of the father of the first affected member." This is, indeed, the case most suggestive of such an explanation among the three cases reported by Cockayne.

The third family showed a condition known as keratoma dissipatum hereditarium in which small, hard, horny papules appear on the hands and feet. In the first generation of the family in which it appeared all the three sons were affected and all the four daughters escaped, and in the second generation all the six sons of

the males were affected and the only daughter escaped, whereas eight sons and four daughters of three females were normal. Cockayne thinks that "the simplest explanation of this phenomenon is that the condition is caused by a gene in the Y-chromosome." Although, similar to the cases of hypertrichosis of the ears, this condition makes its appearance only after puberty has been reached, the evidence is somewhat more suggestive here on account of the fact that there were eight grown-up unaffected sons of females of the first generation and no affected ones. Additional evidence is needed badly before definite conclusions can be drawn.

A compilation of the kind of Cockayne's book of necessity includes a great deal of incomplete and unsatisfactory evidence. The author's presentation, however, is always based on the best available information. In general, the book seems to include all the important literature of the field; of major omissions the reviewer has noted only the important work of Korkhaus on dental anomalies in identical twins. In some instances reference is made to abnormalities of lower mammals similar to those of humans, but many important cases of this kind are not included in the book; for many of those which are given the references to the literature unfortunately are lacking. On the whole, Cockayne's book is a remarkable achievement, and it contains a wealth of information which should stimulate further research. In future editions one might wish for the inclusion of a discussion of the genetics of "normal" skin characters, an authors' index (a serious omission in a work of this type), and, perhaps, a reconsideration of the way in which the material is classified.

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World Potato Varieties

KUHN-ARCHIV: Arbeiten aus den Landwirtschaftelichen Instituten der Universität Halle. Band 33; siebenter Sonderband für Pflanzenbau, *edited by* Prof. Dr. Th. Roemer. Pp. 457. Berlin: Paul Parey, 1932.

ISSUES of Kühn-Archiv are devoted to animal husbandry, agricultural economics, and crop production problems. Contributions on the economic phases of agriculture, it would appear from the tables of contents of previous issues, are likely to have primary or exclusive application to conditions in Germany, but articles on the other subjects are not so liable to this limitation.

This is the seventh volume which has been composed of papers relating to cultivated plants and crop raising problems and methods. The nine articles it contains range in subject from suggestions for reducing farm costs to a study of the physiological specialization of the brown wheat rust. More than 100 pages are devoted to an elaborate tabulation, by H. von Rathlef, of all known potato varieties, giving their origins and interrelationships, together with a descriptive table of fertile-seed strains. A paper by G. Harig on the economical and biological bases for the shifting of wheat-growing regions which has taken place in the United States, and a critical review by M. Hollrung of work on potato diseases from 1840 to the present are perhaps of more general interest. Each of these articles contains some mention of the genetic aspects of the subject considered.

The remaining papers in the volume deal with potato-scab, the quality of certain Rumanian wheat varieties, problems relating to the quality of German wheat, and management costs of roughing-mills.

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THE NATURE OF SUSCEPTIBILITY TO CANCER IN MICE

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THE application of genetic principles to the investigation of cancer reflects the history of that science. These fundamental principles are (1) Pedigree chart (familial transmission of inherited tendencies); (2) outcrossing; (3) inbreeding without selection; and (4) inbreeding with selection. Each of these genetic methods will be briefly discussed.

(1) *Pedigree chart.* Many years ago it became evident that many peculiarities were handed down from one generation to the next. There came into use the tabulation of the data in a chart showing the genetic relationship existing between the various individuals. This was the method mainly employed until the principles enunciated by Gregor Mendel were fully recognized. Since then the emphasis placed upon the pedigree chart has greatly changed. It is increasingly apparent that the proper analysis of the pedigree chart can only be brought about by first considering the conclusions arrived at from the last three general methods of genetics.

(2) *Outcrossing.* The pioneer work of Gregor Mendel was based upon the experiment of crossing two distinct variations of garden peas. After this had been done, additional individuals were produced by mating together these original hybrids derived from the two ancestral stocks. The analysis of the data obtained by this so-called outcrossing, has led to fundamental concepts of inheritance. Two of these concepts are of importance to the proper investigation of cancer susceptibility. Both of these have to do with the proof or disproof of inheritance. The first concept is that if a trend or characteristic is inherited it must show up in a definite number of hybrids of the second filial generation which were originally produced by outcrossing two distinctive individuals—one with the character, the other without it. Further than this the ratio of individuals that have the character to those that do not possess the trait in the two backcross generations must be mathematically consistent with the ratio obtained in the segregating second filial generation. A backcross generation is produced by mating an individual of the first filial generation to a representative of one of the two ancestral stocks. The original application of this genetic principle to the investigation of cancer susceptibility was carried out by Lynch. Very suggestive data are continually coming from her laboratory. The second concept of genetics is that the most positive proof of inheritance of a given unknown characteristic is the demonstration of "linkage." That is, if the unknown trait under consideration is proven to be transmitted together with an already established inherited characteristic, then it must be obvious that the new tendency is also inherited. This technique has been recognized for some time but unfortunately the demands of genetics are too severe—as not all the recognized differential determiners of inheritance (the chromosomes) have been identified by distinct inherited characters. However, some progress in this direction has been made.

(3) *Inbreeding without selection.* A significant advance was made by Little when he started to reduce biological variability by inbreeding. His inbred stock, the dilute browns, is at present well known since Little has sent rep-

*These experiments have been partially supported by a grant from the Josiah Macy, Jr., Foundation.

resentatives of it to several laboratories. After the strain had been inbred, mainly by brother-to-sister matings for a period of several years it became increasingly obvious that there was a high incidence of cancer of the breast in those females that had been used as breeders. The nucleus of this inbred strain was turned over to W. S. Murray who has continued observations on rather a large scale.

The influence of the various physiological functions, such as fertility, fecundity, relative sexual maturity, etc., on the incidence of cancer is now being analyzed and positive facts on this subject can be expected.

(4) *Inbreeding with selection.* By the application of the third principle of genetics, homogeneous or pure individuals can theoretically be expected. By this is meant that a certain degree of biological variability can be diminished thus producing two individuals which are potentially very similar in their physiological activity. The degree of variability can usually be detected in a careful statistical analysis of the data obtained. The technique has one drawback in that it does not take into consideration the possibility that slight genetic changes may be occurring during the process of inbreeding.

Several years ago it occurred to me that inbreeding with selection would produce the ideal situation for the fixation of biological variability. For this purpose I selected my albino strain that had been originally obtained from Bagg. In the twenty-seventh generation of inbreeding I had obtained two sisters, one of which developed carcinoma of the breast at 6.5 months, the other at 15.5 months. Thus I had observed two sisters near the two extreme limits of the age incidence of cancer. The first mouse, No. 13,623 developed cancer at 6.5 months and gave rise to the *A* stock; the other one (No. 13.622) with cancer at 15.5 months produced the A_2 stock. In the *A* line I deliberately selected toward early incidence of cancer by continuing only the descendents of those mice in any given generation that first developed cancer. The A_2 stock was selected by continuing only the descendents of those mice in each generation that lived the longest without cancer or that developed cancer last. The age distributions of cancer of the breast for the two selected stocks are given in Figure 37. It will be noted that there is no significant difference between the two lines.

Discussion

Selection, away from and toward cancer (age incidence) was started in the twenty-seventh generation of an inbred stock of mice. It has been statistically proven that the degree of inbreeding by brother-to-sister mating to which the mice had been subjected before selection began, would be adequate in producing a high degree of genetic homogeneity. Therefore the conclusion seems warranted that "selection within a pure line is ineffectual." This conclusion, originally formulated by Johannsen from his extensive selection experiments on the size of castor beans, has been verified on many different biological materials. It seems likely then that the phenomenon of cancer obeys, to a certain extent at least, one of the fundamental biological laws that have been demonstrated on other biological material.

There has been produced then a "pure line" as to the origin of spontaneous carcinoma of the female breast. Are we even now justified in making a genetic outcross to demonstrate whether this predisposition factor is transmitted according to the principles of mendelian inheritance? Unfortunately we must still answer in the negative. It is more difficult to fix, by selected inbreeding, the hypothetical state of immunity or freedom from cancer than it is to establish a susceptibility to cancer. In order to have a definitely resistant animal one must have the individuals live beyond the so-called cancer-age. To my knowledge, there is not a stock of immune mice in existence that would stand the test of statistical analysis. Great progress has of course been made

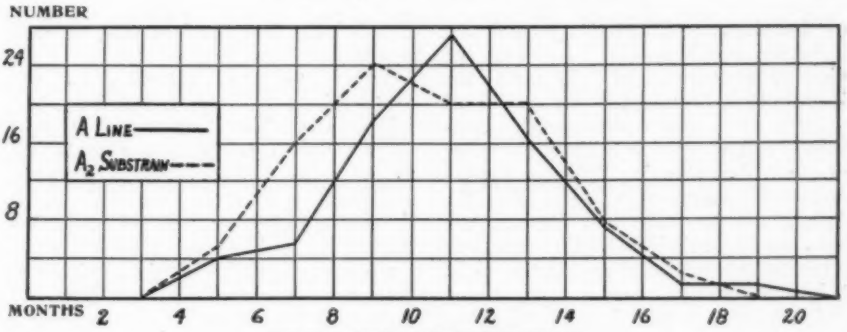

Figure 37

The age distribution of spontaneous carcinoma of the female breast for (1) the *A* stock on the solid line and (2) the A_2 substrain drawn on the dash line. These strains were derived from inbred sisters which differed markedly in age at which cancer of the breast appeared. One line (*A*) was selected for early incidence of cancer; the other (A_2) for late incidence of cancer. The strains are of such great uniformity that selection has not been effective in differentiating them with respect to age incidence of cancer.

in this direction. I have in my own laboratory three stocks, particularly, the individuals of which never develop cancer of the breast. These are the *CBA*, the *JK* and the *N*. In direct descent, the average length of life for these mice is beyond the cancer age. The number of individuals required for a proper statistical study have not yet been available. However, we are slowly trying to produce larger numbers.

Conclusions

1. The phenomenon of cancer obeys certain fundamental biological laws which have been formulated on diverse biological material.

2. Johannsen's principle, "selection within a pure line is ineffectual," applies to the age incidence of cancer of the breast in mice.

3. The expansion of the genetic principle of "outcrossing" applied to the incidence of cancer of the breast is, perhaps, unwise at the present time. More studies on inbreeding should come first.

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The Paths of Growth and Death

GROWTH, *by* the late James Lorrain Smith, M.D., L.L.D., D.Sc., F.R.S., Professor of Pathology, University of Edinburgh, edited by J. S. Haldane, C.H., M.D., F.R.S. Edinburgh and London, Oliver and Boyd, VII + 135 pages, price, 6/3. 1932.

IT is generally known that growth in higher animals is essentially a multiplication of cells; that cell division in the body normally leads not only to increase in size but also to differentiation and specialization of cells for various physiological functions; that intense specialization leads to the loss of capacity of the cell to divide, which in turn means the death of the cell after a shorter or longer interval. Lorrain Smith's thirteen essays in this book elucidate and illustrate these facts from the rich experiences of a distinguished pathologist and a thoughtful philosopher. As a pathologist, Lorrain Smith's illustrations are mainly from the field

of histology and pathology, and are naturally dominated by the point of view of the pathologist. As far as the individual is concerned the paths of growth and development must necessarily lead to disease and death. The geneticist has cheering thoughts for the future of the race; but as regards the future of the individual he can not help but be reminded of Schopenhauer's advice never to cheer up for the worst is yet to come.

Many facts emphasized in this book while well-known, are not widely known or well-defined. The cells of the tissue of the mouse are about the same size as those of the elephant. The size of animals is thus governed almost entirely by their cell numbers. Growth in living organisms differs from "growth" in inanimate bodies in that in the former there is no gathering of units to join it from outside sources. Growth in the living organism is a procession of cell-units in which each member in its turn disappears in producing its successors. One is, of course, reminded of the analogous case of population growth in which the older generation is disciplined by the younger generation. Growth of populations of organisms is thus likewise a procession in which each member ultimately disappears in producing its successors.

In one sense growth continues throughout life. It is true that growth is most active at the beginning, before the master activities of gland, muscle, and nerve have been established. These activities, once they have come into play, continue throughout the remainder of life, while the impulse to grow has ceased. But the structures thus formed have to be maintained, and in case of injury repaired, by a continuous growth process. It is generally known that the latent growth impulse is easily awakened to intense activity by injury or irritation as well as by the periodic endocrinal "tides of life." Growth is thus the creative and maintaining principle of the body and of life, as well as the path to death.

This intense reawakening of the growth impulse in cases of irritation, injury, and other physiological changes often leads to considerable trouble due to its uncontrollable character as in malignant and other tumors. Here there is an interesting disagreement between J. S. Haldane, the editor of these essays, and Lorrain Smith the author. While Smith favors the view that growth in a malignant tumor has lost its co-ordinated character owing to an injury to chromosomes, this injury being transmitted as a mutation from cell to succeeding cells, Haldane believes that malignancy is due to the presence of an ultra-microscopic virus which can only grow within the living body of a particular kind of cell, and can usually gain a footing only under specially favorable conditions which can be compared with the influence of inhaled silica particles in facilitating tubercular infection of the lungs.

In the stimulating supplementary chapter by J. S. Haldane, the eminent physiologist, special emphasis is given to the doctrine of the "organism as a whole" as contrasted to "vitalism" on one hand and "physico-chemical realism" on the other. "It was Lorrain Smith's ideal to make the distinctive conception of life the basis of pathology, just as it has been my own ideal to make this conception the basis of physiology."

This book on growth is on the whole a good antidote to the one-sided enthusiasms generated by mere biometric and mathematical analysis of physical growth.

The well-balanced book on growth is still awaiting an author, whom it is hoped that our state of differentiated and specialized scholarship has not rendered incapable of synthesizing and presenting all sides of this complicated and fascinating subject.

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INHERITED ANOMALIES OF METABOLISM

Part II

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GOUT, although long regarded as due to too ardent a devotion to Epicurean delights, has also long been looked upon as occurring in individuals with a hereditary predisposition to such an affliction. Osler[7] states that between 50 and 60 per cent of the patients suffering from gout gave a family history of the disease. Males were more frequently affected than were females. It has been looked upon as due to a hereditary basis which manifested itself in a cellular sensitization, the actual disease being precipitated when the sensitized cell encountered the appropriate protein.[4] Vascular endothelial poisoning results from this, though just how this would be productive of the abnormal metabolism which permits of large amounts of uric acid and sodium biurate being deposited about the joints is difficult to say.

The mode of transmission of gout will probably appear quite erratic, if the final appearance of clinical symptoms is dependent upon sensitization. The family histories reported are too meager to give any adequate idea of the mode of transmission; some show more than one generation affected, others show several children in one generation affected.

Two instances of the first type of history are (1) a man and his great-grandson of 14 suffering from gout; and (2) a man and his son affected. The second type of history is illustrated by such records as (1) two sisters affected at the age of 30 with uric acid deposits along the extensor tendons of the hands. Orbison's[6] record of a man and his wife and eight of their nine children with gout might fit in with either a dominant or recessive mode of transmission.

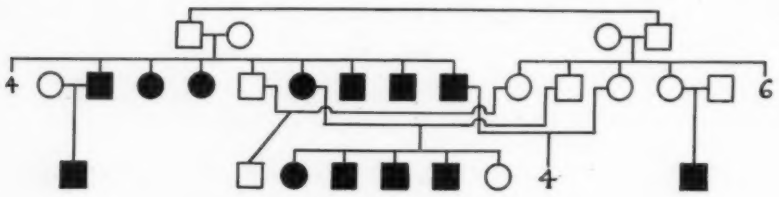
Research is needed to clear up many points. It is quite possible that many persons show the high uric acid content in the blood who have not developed symptoms; just as many persons may have a blood sugar above normal and sugar in the urine without being aware of the fact that they have diabetes.

Alkaptonuria

Alkaptonuria, together with cystinuria and pentosuria, has been called by Garrod,[1] "an error of metabolism." It is characterized by the appearance in the urine of the acid, alkapton, which causes the urine to turn dark, either upon standing, or upon the addition of alkali. The formation of this acid is apparently dependent upon a pair of recessive factors, inasmuch as it occurs in children in the family in which there is seldom any other history of the disease, and it occurs in families in which there is an excessively high rate of consanguineous marriages. Of the twelve families in which it occurred, six or 50 per cent of them stated that the parents were first cousins. This is an incidence of consanguinity that is well over 100 times that found in the general population. There were six families with two children affected, four with three, and two with four children. In only one instance did parent and child have the disease.

Cystinuria

Families in which cystinuria has appeared are relatively rare. Again it is difficult to suggest a mode of inheritance, or at least, which is the commonest mode of transmission shown by this condition. The fact that a person may be excreting cystine crystals in the urine without having any symptoms from the condition, makes it possible that all cases in which the parents of the affected offspring were said to be free, were in reality instances of direct transmission from parent to child. There may be different modes of transmission in this disease as in so many others in man.



INHERITANCE OF CYSTINURIA

Figure 38

While this complicated series of cousin marriages demonstrates the inheritance of Cystinuria, conclusions with regard to the mode of inheritance must await more data. After Thin.

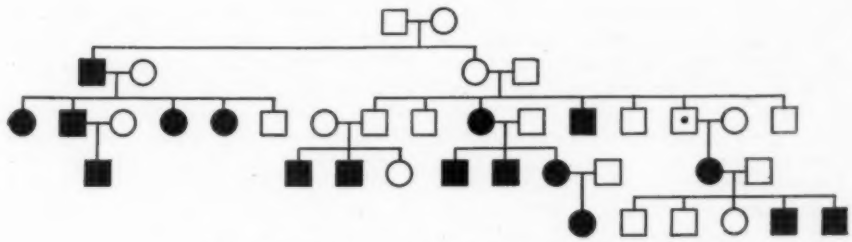
Records illustrative of what might be the recessive mode of inheritance are those of two children in the family with the disease; or three boys out of five with it, all five showing excess of oxalates in the urine as well; or still another family in which two sons were affected.

The other type of transmission direct from parent to child is shown in the family in which three sisters, and the two daughters of one of them were affected. This of course might be recessive as well as dominant transmission. But when we come to a record of three generations affected in the direct line of descent with such a rare condition, then it is almost outside the realm of chance that recessive transmission was involved in this case. Three children in the third generation died of the disease, and at autopsy the organs were found to be infiltrated with cystine crystals. The incidence of this condition in the population is given by Lewis,[8] who examined 10,534 patients for it, and found 18, or one in every 585 persons. Two of the 18 were brother and sister. A most remarkable record of this disease is given by Thin,[9] which will be quoted in detail, since it furnishes such a striking evidence of the fact that such a condition is dependent upon heredity. It concerns the children of two half-brothers who were not regarded as being cystinuric, (Figure 38). The first of these men had twelve children, of whom seven were known to have cystinuria. The second had ten children none of whom developed the disease. Of the seven who developed it, one was a female *A*, who had had litholopaxy performed three times between the ages of 27 and 45, for cystine calculi. The second, also a female, *B*, had suffered from renal colic since she was 17, and had frequently passed cystine calculi. The third, also a female *D*, had always suffered from renal colic, and had died a few days after operation for the removal of a cystine stone from the left kidney. It will be noted that she married the unaffected son of her father's half brother. She had five children, of whom three boys and one girl were sufferers. Two, *J* and *K*, had renal colic and cystine crystals in the urine, *K* also had a calculus in the left ureter; the other two, *L* and *M*, did not have colic, but had cystine in the urine constantly. *E*, *G*, and *H* of the second generation were all males with cystinuria, and had suffered no inconvenience so far from the disease. *F* was also a male, who had had litholopaxy done nine times for the removal of cystine calculi. One of these brothers *H* had a son who also had cystinuria.

Oddly enough there were three marriages between the children of these two half brothers. An unaffected son *C* of the first brother married an unaffected daughter of the second, and had by her a son with cystinuria. *D*, who had four affected children, had married an unaffected son of her father's half brother. One of the affected men, *G*, had married a daughter from this family, but their four children were so far normal. A fourth daughter in the unaffected family of ten married a relative, and produced a son with cystinuria. Thus there were seven cases in the first generation, and six cases in the second. The fact that of the four marriages in the second generation producing affected offspring three were between relatives both coming from the affected stock might suggest that this disease was due to a recessive factor in this family at least.

Pentosuria

Like the other two conditions mentioned, pentosuria is apparently inherited. The majority of cases occur in children whose parents do not show the defect, and whose brothers and sisters are not affected. This would suggest that the metabolic error was due to recessive factors, possibly to several pairs, owing to the rarity of finding more than one in the family with it. This idea of recessiveness of the determining factors is still further strengthened by the fact that many of the re-



FOUR GENERATIONS OF UROBILINURIA

Figure 39

This strange abnormality is effected by the position of the individual. In an upright position the patient's metabolism is abnormal, i. e., urobilin is excreted. When the same person is lying down the urine is normal. It is suggested that this peculiar situation may be accounted for by a persistance of fetal blood vessels, which are closed when the patient is in a procumbent position, forcing the blood through the liver which organ eliminates the urobilin.

ported cases occur in those of Jewish extraction, among whom the number of consanguineous marriages is apt to be unduly high. Margolis[5] in 1929 stated that up to that time 72 cases had been reported in the literature, and that one-third of these occurred in nine families, thus demonstrating the hereditary nature of the disease.

Three families were found in which two of the children were affected, all others in the family normal. One family had father and son affected; one had three generations affected; and a third had three generations affected, namely two sisters, their two brothers, their father and his mother.[2] The families in which more than one generation are affected, with a condition that appears to be so rare, probably exemplify a dominant, not a recessive mode of inheritance.

Steatorrhea

This condition is so rare, that I have found only three cases mentioned in the literature. For some reason the fat is not utilized by the body and is excreted in the stools unchanged. Just where the original error lies, whether in the pancreas which fails to secrete its enzymes for fat digestion, or in the bile, which assists in fat digestion, has not been worked out. Two of the three cases reported were in children whose parents were related. It is possibly due to one or more pairs of recessive factors.

Porphyrinuria

This extremely rare disease of which there are not two dozen cases reported in the literature, is characterized by the production of large quantities of the pigment known as porphyrin, which are deposited in the tissues, the bones and the teeth, and excreted in the urine. The result of this deposition is that the patient has purplish pink teeth, bones that throw a shadow when the hand is held before a strong light, a urine that is deep red in color, turning brown on exposure, and a sensitivity to sunlight that makes life a burden. The exposed parts of the body break out into large blisters that soon ulcerate, leaving deep scars as they heal. In some cases the destruction of tissues is so great over a period of years that large parts of the nose and ears have been eaten away. Although this condition has been found so seldom, there is strong evidence in favor of its being inherited, inasmuch as the cases are grouped in families. It is probably due to a pair of recessive factors.

I have encountered two instances in which the child was the only one in the family affected; two in which three of seven children were affected; another in which first cousins were the victims; and another in which two children and their first cousin had the disease. There were no instances of consanguinity reported in these six families.

Urobilinuria

The only record of this metabolic defect which I have found listed as occurring in more than one member of the family is that by Steensma[8] in which there were seventeen members affected through four generations. The very interesting thing about this family was that it was an orthostatic urobilinuria, that is, the urine was free of urobilin if excreted when the patient was lying down, but showed the presence of urobilin if excreted when he was in the upright position. It will be noted from Figure 39 that three times it was passed on by those who were listed as free from it. In two of those cases, however, the person so listed was dead so that it was impossible to examine the urine. They might have been free or they might have been affected. In the remaining case, namely the unaffected male whose daughter and two grandsons were affected, the urine was examined and the result was negative. One is led to question whether the condition which was at the basis of the defect was so mild in this person as to produce insufficient urobilin for detection, whether there was a mistake as to time of collection of the urine or if the condition can be passed on by those not exhibiting the actual defect themselves. Steensma[8] feels that inasmuch as posture affects the appearance of the urobilin in the urine, some anatomical defect is at the basis of the condition, and he postulates a ductus venosus that is not completely obliterated, so that blood passing from the intestine is capable of escaping into the general circulation through the old fetal route. Conditions when the patient is in the upright position might favor the passage of blood through the ductus venosus, while the recumbent position might interfere with it, forcing all the blood through the portal circulation into contact with the liver cells, before entering the general circulation.

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A Glossary Of Genetic Terms

GENETICS has developed so rapidly that many terms in common use in genetic literature are not yet incorporated in the dictionaries. Many people who are interested in heredity are bothered by such words, for which no definition can conveniently be found. For this reason, it is proposed to publish occasionally a glossary of terms which would not be readily understood and which are not to be found except in new unabridged dictionaries. It is realized that these definitions will probably not meet with universal approval and comments and suggestions will be welcomed.

BACKCROSS—Cross of a hybrid to one of the parental forms.

CHARACTER (a contraction of characteristic)—A term used, often rather vaguely, to designate any form, function, or feature of an organism. The Mendelian characters of genetics represent the end-products of development in which a definite gene, or genes, have a decisive effect. "The constant and unchanging thing, therefore, is the factor (gene) itself rather than the character, and the unity which Mendel observed lies rather in this underlying factor than in the visible, and perhaps variable, character which it produces."—Sinnott and Dunn.

CONJUGATION—Side-by-side association of homologous chromosomes previous to formation of genetics.

DIPLOID—Having two sets of chromosomes. Body-tissues of higher plants and animals are ordinarily diploid in chromosome constitution. See *Somatic*.

DOMINANT—A character possessed by one of the parents of a hybrid, which appears in the hybrid to the exclusion of the contrasted character from the other parent (the recessive). Thus in a cross of green- and yellow-seeded peas the first generation has yellow seeds. Yellow is dominant and green is recessive, being transmitted but not appearing in the presence of the factor for yellow.

FACTOR—Same as *Gene*.

F_1—(Pronounced eff-one). The first filial generation. The offspring of a given mating.

F_2—The second filial generation. Produced by intercrossing or self-fertilizing the F_1. The inbred grandchildren of a given mating.

GAMETE—A reproductive cell of either sex; e. g. sperm or ovum.

GENE—(1) The unit of inheritance, which is transmitted in the germ cells, and which by interaction with the genic and cytoplasmic complex controls the development of a character. The genes are arranged linearly in the chromosomes. (2) "The physical basis of heredity"—or more figuratively, the atom of the genetic molecule.

HAPLOID—Having the reduced number of chromosomes, as in germ cells, as distinguished from from the diploid or double number of chromosomes in normal somatic cells.

HETEROZYGOUS—Containing both genes of an allelomorphic pair, or two genes of an allelomorphic series. Heterozygous individuals generally resemble the individuals homozygous for the dominant character, but they transmit the recessive to half their offspring.

HOMOZYGOUS—(1) An organism formed by like germ cells; (2) An organism is said to be homozygous for a given character when all the germ cells transmit identical genes for this character. This is the most frequently used meaning of the term.

LINKAGE—Association of genes in inheritance, due to the fact that they are in the same chromosome.

MONOZYGOTIC—Originating from a single fertilized egg cell, which in the course of subsequent development has given rise (by fission) to two or more individuals. Twins (or triplets, etc.) of such origin are, barring mutations, genetically identical.

MUTATION—Where a heritable variation begins. A sudden variation in an inherited character.

PARTHENOGENESIS—The development of a new individual from a germ cell without fertilization.

POLYPLOID—Normal body cells of the higher plants and animals have two sets of chromosomes (see *Diploid*). Polyploids are forms having three or more of these basic chromosome sets.

RECESSIVE—See *Dominant*.

REDUCTION DIVISION—The division preceding the formation of gametes, in which the chromosome pairs separate, and the chromosome number is reduced to half the somatic number.

SEGREGATION—Separation of allelomorphic genes at meiosis.

SELFED—Self-pollinated.

SOMATIC—Resembling body tissues in having a paired set of chromosomes, one set from the female parent and one from the male, as contrasted with germ cells having a single set of chromosomes.

TRIPLOID—An organism characterized by having three times the reduced primary chromosome number.

Comments from the Questionnaires

To gain some direct information regarding the feeling of members toward the JOURNAL *a questionnaire was sent with the 1934 bills. The responses have been most interesting and very gratifying. Possibly when the returns are all in there may be enough of general interest to justify a note in the* JOURNAL *as to the division of opinion regarding such controversial subjects as the glossary, which present returns indicate is about equally valued and despised. The more general comments under "remarks" have been, with few exceptions, most enthusiastic and encouraging. Some of them are here reproduced.*

"I think you are doing excellently well. Your field is a big one. I feel that articles which are mere reports on minor points (such as the announcement of a new hereditary factor) should be kept relatively brief, while matter of fundamental theory, technique, or work with important implications should be quite fully covered."

"I enjoy the JOURNAL very much but am uncertain as to its purpose. It is too small to present detailed researches or observations. Why not recognize this? The articles listed above are very interesting but I would prefer them in other journals where as much as eight or ten pages are required."

"I am undecided; I hear the JOURNAL criticized for being too popular, (general) not technical. I believe its mission is to give facts of research and opinion to those not highly trained technically in genetics. I find it *now* the *most useful* journal in teaching genetics."

"I am satisfied *as it is!* I hope the questionnaire won't stampede you into any radical change."

"One of the most essential things at present is a suitable publication outlet for research and I would favor curtailing other features if necessary to give space to research articles of permanent value. I appreciate, of course, the educational needs and value of articles for public discussion of questions having popular interest. Short articles of this kind are likely to have a wider appeal than long ones."

"I approve the present trend to encourage the study of human heredity as well as that of economically important plants and animals."

"Along with results of research more articles discussing present situations and problems."

"Don't wander further into the field of sociology or economic aspects of eugenics. Opinion predominates over ascertainable fact there, and the resulting controversies settle nothing. The present policy in this is about right but should certainly not deviate any *further* into this field, no matter how enthusiastic some advocates of complete social planning of all affairs may become."

"For my purpose, I prefer more space given to the plant side. The animal side is getting six or more times as much space as the plant side. Condense the papers some on animals; also some of the long ones on plants. Give us more wheat, less of the chaff."

"While I value the JOURNAL highly because it does cover a broad field, I would like to see more short articles on inheritance in crop plants than have appeared during the last year or two."

"I like the JOURNAL just as it is. I shall continue to pull in my belt so that I may subscribe for it, be the depression ever so long. I like to read the JOURNAL, but I'd continue to subscribe for it if it bored me stiff because I think the people behind it are engaged in a most important job, and I consider it a privilege to help a tiny bit."

"Prompt publication of issues (congratulations on the effort during the past year to catch up with the calendar). A more impersonal attitude on the part of some book reviewers."

"Hell, I don't know, I'm neither a scientist, nor a journalist. I've been reading the JOURNAL since it first came out. I'm just a bum country lawyer (once for 20 years a judge). Reading the JOURNAL gives me a chesty feeling of going along with the big boys of science. There is something impersonal and real about your work as compared for instance to the dirty businesses of money making and politics."